# Clinical use of C-reactive protein for the prognostic stratification of patients with ischemic heart disease

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**C-reactive protein (CRP), the prototypic acute phase reactant and a sensitive marker of inflammation, consistently predicts new coronary events, including myocardial infarction and death, in patients with ischemic heart disease. The data are very consistent with regard to the long-term outcome, but in many studies are also significant for in-hospital events. The predictive value of CRP is, in the majority of the studies, independent of and additive to that of the troponins. Moreover recent data suggest that CRP may be a reliable marker of the risk of restenosis after percutaneous coronary interventions and that its levels can be modulated by statins. Taken together, all these data suggest that CRP, probably with different cut-offs, should be used as a marker of risk and as a guide to therapy in patients hospitalized for acute coronary syndromes and in outpatients suffering from ischemic heart disease.**

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Although the risk of death and myocardial infarction (MI) after a first coronary event is still relatively high, with a probability of death of about 6-8% at 4 to 6 months[1,2], prediction of new coronary events in patients with ischemic heart disease is difficult. Increasing age, a low ejection fraction, the number of diseased vessels and diabetes are all associated with death and MI, but the sensitivity and specificity of these risk factors are low. Furthermore, a low ejection fraction, multivessel disease and advanced age may identify a subgroup of high risk patients, but in patients with a low to moderate risk the prediction of future events on the basis of these clinical risk markers is poor.

Recently accumulated data demonstrate that inflammation plays an important role in the pathophysiology of ischemic heart disease, suggesting that markers of inflammation may be reliable predictors of the short- and long-term risks and may have an incremental value with respect to other risk factors. This is particularly true for C-reactive protein (CRP), a prototypic acute phase reactant, the levels of which rapidly rise after an inflammatory stimulus. Depending on the intensity of the stimulus, even a several hundred-fold increase may occur[3,4]. Moreover CRP is not consumed to a significant extent in any process, and its clearance is not influenced by any known situation. Therefore its concentration is dependent only on the rates of production and excretion. The half-life of CRP is 19 hours, making its detection in blood easy. In human beings the major inducer of CRP is interleukin (IL)-6[4] which, in turn, is induced by tumor necrosis factor-$\alpha$, IL-1, platelet-derived growth factor, antigens and endotoxins. CRP is a molecule involved in defense mechanisms forming part of the so-called innate defense. CRP binds to monocytes, macrophages and neutrophils and activates the complement system cascade favoring opsonization of the intruder molecules. CRP may also modulate the immune response, enhancing the activity of T and B lymphocytes and of natural killer cells. CRP also enhances monocyte and macrophage production of oxygen free species and of tissue factor. The known CRP properties are not unique to this molecule. Other molecules or systems have similar characteristics. However, considering its numerous functions, besides being an important modulator of the inflammatory response, CRP also plays other relevant roles as for example in cardiovascular disease. CRP is indeed an almost ideal marker of disease activity in many inflammatory and infectious diseases. Furthermore it is a pro-

tein that is not released or degraded *ex-vivo* hence being stable in blood samples even after prolonged storage at room temperature and delayed analysis. Finally, easy to use, inexpensive and precise kits allowing reproducible CRP titration are commercially available (a WHO standard for CRP exists).

## C-reactive protein and the risk of cardiovascular events in unstable angina and non-Q wave myocardial infarction

**Short-term outcome.** In 1994 Liuzzo et al.[5] had shown a significant association between CRP levels and prognosis in severe unstable angina. An admission CRP level > 3 mg/l (90 percentiles of normal) was associated with an increased risk of the combined endpoint recurrent angina + death + MI in 31 patients with severe Braunwald class IIIB unstable angina. In this study patients with CRP levels < 3 mg/l were free of events except for 2 who presented an elevation in CRP concentrations after admission. Eighteen of 20 patients with CRP levels > 3 mg/l had events. A CRP level > 10 mg/l had a 100% sensitivity for in-hospital cardiovascular events. This study demonstrated that CRP may distinguish unstable angina patients into two groups: one with low CRP levels and low in-hospital risk and one with high CRP levels and high in-hospital risk. Although a trend was present, because of the small number of patients an association with the hard endpoint death and MI was not demonstrated. On the other hand, in a recent study[6] including a larger population (251 patients) with unstable angina, CRP levels were independently associated with the combined in-hospital risk of death + MI. In this study a CRP level > 19 mg/l was associated with a 5-fold increase in the risk of death + MI. Even Morrow et al.[7] have observed a significant association between CRP levels and the risk of death at 14 days in the TIMI 11A substudy including 437 patients with unstable angina and non-Q wave MI. For a CRP level > 15 mg/l the sensitivity and specificity were 86 and 76% respectively. However, in other studies (Table I)[5,7-17] no association was found between CRP levels at entry and the risk of death and MI. As some of these studies were large multicenter trials[1,17] it is possible that the positive results observed in the aforementioned studies were due to chance, because of the smaller number of patients enrolled or, more probably, to stricter entry criteria: studies including a large number of patients with unstable angina lower than Braunwald class III and thus a less severe prognosis, or conversely, including patients with non-Q wave MI, in which the prognosis is largely dependent on the extent of myocardial damage, may not permit correct evaluation of the prognostic value of CRP. Besides, the patient status at baseline (before the index unstable angina or non-Q wave MI event) should be considered as, regardless of the inflammatory status, patients with severe left ventricular dysfunction are likely to have the worst prognosis[18].

**Long-term outcome.** In 1995 the ECAT study was published[19]: in this study 2300 patients with either stable or unstable angina were enrolled and followed for 2 years. Major cardiovascular events were significantly associated with the levels of fibrinogen and, with a borderline significance, with those of CRP. However, in 1997 the same group published new data obtained by an ultrasensitive method[10]: in this study patients in upper quintiles of the distribution of CRP levels showed a 3.5-fold increase in the risk of major cardiovascular events during follow-up.

In an analysis of the FRISC study population, Toss et al.[9] studied 915 patients independently of their troponin status and found that, for unstable angina and non-Q wave MI patients, the mortality rate at 150 days was 8% in case of elevated levels of CRP (> 10 mg/l) vs 2% in case of CRP levels < 2 mg/l. These data were confirmed in a recent study with a follow-up of 4 years[16], in which CRP levels > 10 mg/l were associated with a 16.5% mortality risk vs 5.7% in patients when CRP levels < 2 mg/l (adjusted relative risk 2.6, 95% confidence interval 1.5-4.6). We have more recently reported the results of a 1-year follow-up study including 53 patients with similar characteristics: patients were drawn at entry, discharge and at 3 and 12 months of follow-up[14]. This multivariate analysis also including fibrinogen levels, age, family history, diabetes and hypertension demonstrated that elevated (> 3 mg/l) CRP levels at discharge are an independent predictor of new unstable ischemic events including death, MI and new hospitalization for recurrent unstable angina, with an odds ratio of 8.7. This study also demonstrated that elevated CRP levels persisted for at least 12 months in up to 39% of patients, suggesting a persistent inflammatory stimulus in many unstable patients. In these studies only troponin negative patients were enrolled. Thus, the influence of myocardial damage on CRP levels was ruled out. In patients with high CRP concentrations, coronary angioplasty and coronary artery bypass grafting (CABG) did not modify the recurrence rate of ischemic events within 1 year of follow-up. This is in line with the observations that elevated CRP levels (> 3 mg/l) are associated with an increased risk of restenosis and of acute complications after balloon angioplasty in both stable and unstable angina and that up to 8 years following CABG, elevated CRP titers (> 3 mg/l) are associated with an increased risk of new ischemic events[20,21]. In a study including patients with unstable angina and non-Q wave MI and with a follow-up lasting 90 days, Ferreiros et al.[15] confirmed that elevated levels of CRP are associated with an increased risk of coronary events. CRP levels in blood samples taken at entry and at discharge were significantly associated with future events but the latter were better predictors of events (CRP at dis-

**Table I.** C-reactive protein levels and outcome in unstable angina.

| Author | Patients | Primary endpoint | Dosage method | Limit of normal (mg/l) | Results |
|---|---|---|---|---|---|
| Liuzzo et al.[5], 1994 | 31 pts with UA in Braunwald class IIIB | Intrahospital acute MI, cardiac death, urgent revascularization | Nephelometric/ELISA | 3 | 2 (18%) events in pts with CRP < 3 mg/l, 18 (90%) events in pts with CRP > 3 mg/l ($p < 0.05$) |
| Oltrona et al.[8], 1997 | 140 pts with UA in Braunwald class IIIB | In-hospital cardiac death, Q and non-Q wave MI, revascularization | Nephelometric | 10 | 101 pts with normal and 39 pts with abnormal CRP levels: no significant difference in events (28 vs 13%); 107 pts without events, 33 pts with events: no significant difference in CRP levels (median 5 vs 3 mg/l); at Kaplan-Meier analysis, no significant difference in survival |
| Toss et al.[9], 1997 | 965 pts of the FRISC I study (UA and non-Q wave MI) | Death and/or MI at 5 months | Turbidimetric | No data | Tertiles of CRP (< 2, 2-10, > 10 mg/l); higher RR (3.46) of death in the uppermost vs the lowest tertile (but not for the combined endpoint death and/or MI) |
| Haverkate et al.[10], 1997 | 2121 outpatients with UA, SA | Sudden death and fatal and non-fatal MI at 2 years | Ultrasensitive ELISA | 3.6 | Quintiles of CRP; the correlation events-CRP levels was significant; one third of events in the upper quintile (> 3.6 mg/l); RR 2 times greater in top quintile vs the first 4 (27 vs 46 events). No difference in CRP levels between UA and SA (geometric mean 1.7 mg/l) |
| Morrow et al.[7], 1998 | 437 pts of the TIMI 11A study (UA and non-Q wave MI) | Death at 15 days | Nephelometric | 1.55 | 106 pts with CRP levels > 1.55 mg/l: 6 deaths (5.6%); 329 pts with CRP levels < 1.55 mg/l: 1 death (0.3%). Significant difference in CRP levels between event and non-event pts (mean 7.12 vs 1.29 mg/l), additive prognostic value with troponin T |
| Rebuzzi et al.[11], 1998 | 102 pts with UA in Braunwald class IIIB | MI at 3 months | Nephelometric, ELISA | 3 | 24 vs 4% occurrence of MI for CRP > vs < 3 mg/l ($p < 0.05$) |
| Montalescot et al.[12], 1998 | 68 pts of the ESSENCE study with UA and non-Q wave MI | Death, MI, recurrent angina and revascularization | Immuno-nephelometric | 5 | No significant differences in CRP levels between pts with or without an endpoint at 14 days (mean levels 8.0 vs 8.6 mg/l) |
| Verheggen et al.[13], 1999 | 211 pts with UA in Braunwald class IIIB | In-hospital refractory UA | Nephelometric | 6 | CRP levels higher in refractory angina group (76 pts, 36%) vs symptom free group (135 pts, 64%) (geometric mean 3.36 vs 2.36 mg/l); quartiles of CRP [OR 2.19 highest (CRP > 6 mg/l) vs lowest (CRP < 1.2 mg/l)] |
| Biasucci et al.[14], 1999 | 53 pts with UA in Braunwald class IIIB | Acute MI, recurrent instability, death at 1 year | ELISA | 3 | 26 pts with CRP levels > 3 mg/l, 27 pts with CRP levels < 3 mg/l; 18 (69%) events for CRP levels > 3 mg/l, 4 (15%) events for CRP levels < 3 mg/l ($p < 0.05$) |
| Ferreiros et al.[15], 1999 | 105 pts with UA in Braunwald class IIIB | Total death, MI, refractory angina during the first 90 days | ELISA | 15 | CRP levels > 15 mg/l at entry predict late outcome (90 days), OR 5.18: 75 pts with CRP levels < 15 mg/l, 26 (34%) events; 30 pts levels > 15 mg/l, 22 (73%) even CRP levels > 15 mg/l at discharge predict late outcome, OR 20: 26 (79%) vs 8 (15%) events. At Kaplan-Meier analysis 90 vs 25% 90 day survival for CRP < vs > 15 mg/l |
| Lindahl et al.[16], 2000 | 917 pts with UA | Cardiac death during a follow-up of 37 months | Turbidimetric | 10 | CRP higher in death vs survivors (13 vs 5 mg/l). Tertiles CRP: < 2 (314 pts: 18 events, 6%), 2-10 (294 pts: 23 events, 8%), > 10 mg/l (309 pts: 51 events, 17%). Kaplan-Meier analysis: upper tertile cardiac mortality in follow-up period was higher vs middle and lower ones (RR 3) |
| Heeschen et al.[17], 2000 | 1081 pts with UA in Braunwald class IIIB | Death, MI at 30 days and 6 months | Nephelometric | 10 | Quintiles of CRP (< 2.8, 2.9-5.3, 5.4-9, 10-22, > 22). CRP levels are not predictive for early prognosis (48-72 hours). 4th e 5th quintile pts had a significantly higher event rate at 30 days (14 vs 7.6%) and at 6 months (18.9 vs 9.5%) vs the other three quintiles |

CRP = C-reactive protein; MI = myocardial infarction; OR = odds ratio; pts = patients; RR = relative risk; SA = stable angina; UA = unstable angina.

charge odds ratio 20.89). In this study a cut-off value of 15 mg/l (no high sensitivity-hs CRP method used) was chosen on the basis of receiver operator characteristic curves; refractory angina, death and MI were considered as events. Recently Heeschen et al.[17] have published a retrospective analysis of the data of the CAPTURE trial. In this paper, CRP levels > 10 mg/l were predictive of cardiac risk (death and MI) within 6 months (18.9 vs 9.5%), independently of the troponin T status.

## C-reactive protein and troponins

Troponins (T and I) are excellent markers of cardiac risk in unstable angina and non-Q wave MI. This raises the doubt regarding the additional value of CRP for the prognostic stratification of these syndromes. The first studies to address this issue were published in 1998. Morrow et al.[7], in a substudy of the TIMI 11A, showed that CRP and troponin T were additive in unstable angina and non-Q wave MI. In particular, low and negative levels of CRP were associated with a less than 1% risk of death at 14 days vs 9% for high CRP concentrations (15 mg/l) and early positivity of bedside troponin T. Rebuzzi et al.[11] have studied 102 patients with unstable angina and confirmed that seronegativity of both markers (troponin T and CRP) is associated with a very low risk of MI (< 2% at 3 months) and that CRP is useful for the risk stratification of patients with negative troponin T, 15% of which, all with elevated CRP levels, had an MI at 3 months. More recently, other studies have investigated the additional predictive role of CRP as associated with that of troponins. In particular the large multicenter trials FRISC and CAPTURE have found, in retrospective analyses, that the CRP predictive value is independent of the troponin T status. In particular, in the CAPTURE study admission levels of CRP were independent predictors of both cardiac risk (death and MI) and repeated coronary revascularization; in both studies the association of high CRP and troponin T levels was confirmed as a strong predictor of future events. Conversely, the association of low and/or negative CRP and troponin levels was suggestive of an excellent prognosis[16,17].

## Practical considerations

**Value of C-reactive protein as a prognostic marker in unstable angina and non-Q wave myocardial infarction.** Available data strongly recommend the use of CRP as a prognostic marker in patients with unstable angina and non-Q wave MI. The data are very strong and consistent for the mid to long-term prognosis, for which, the relative risk observed in different studies ranged from 2.3 to 20. The data are less consistent for the in-hospital prognostic stratification of these patients. It is possible that different criteria of enrollment might have weakened the prognostic value of CRP in this setting; however patients with only Braunwald class IIIB unstable angina and no sign of myocardial damage seem to be those in whom CRP levels offer the greatest contribution even for the in-hospital risk stratification. When studying patients with acute coronary syndromes, no value should be discarded as too high because, following stimulation, CRP levels can increase a thousand fold and there is evidence that in some patients constitutional hyper-responsiveness might lead to very high CRP levels even following mild stimuli[22]. Of course, in the presence of overt inflammatory and infectious disease the data should be interpreted cautiously, and possibly (long-term stratification) CRP titration repeated at least 2 times after the underlying disease has resolved.

**When to sample?** The data available in the literature are mainly based on samples taken at admission. Clearly, this is the best sample for the in-hospital risk stratification of such patients. The two studies in which samples were also taken at discharge[14,15] suggest that CRP levels within these samples are better predictors of the mid to long-term prognosis than those at admission. This is probably due to the fact that discharge levels more closely reflect the baseline inflammatory status of the patients and thus their intrinsic risk due to the inflammatory activity. Conversely, samples taken at entry may largely reflect the extent to which the acute phase reaction is associated with the acute ischemic or necrotic event. However, the ever more widespread policy of treating patients with severe unstable angina invasively and of discharging them soon after a percutaneous coronary intervention (PCI) may induce the same acute phase reaction effect even in the pre-discharge samples. Thus, for all purposes, it is reasonable to assess the CRP levels at entry. When possible, blood sampling at discharge and 1 to 3 months later may be useful, because it is likely that the highest risk of future events is confined to patients with persistently elevated levels of CRP.

## C-reactive protein and percutaneous coronary interventions

PCI are nowadays the leading treatment for acute coronary syndromes accounting for more than 50% of all invasive treatments in these syndromes. In spite of major advances in the technique, such as the use of stents and glycoprotein (GP) IIb/IIIa inhibitors, at least 10% of patients submitted to a PCI are expected to develop restenosis within 3 to 6 months. None of the classical risk factors nor any other procedure-related parameters, with the exception of the final lumen gain, have been found to be useful as predictors of restenosis. The availability of a reliable and simple marker of restenosis before the procedure would be of great interest for the intervening cardiologist, as stents and GP IIb/IIIa in-

hibitors are expensive and may have limitations such as in-stent restenosis or bleeding. CRP has been shown to be an independent predictor of early complications and of late restenosis in balloon angioplasty by Buffon et al.[20], with a relative risk of restenosis equal to 6.2 for CRP levels in the upper tertile vs those in the lower tertile. As in this study only balloon angioplasty was performed (in a population of stable and unstable patients), it is important to observe that in two other studies[23,24] CRP levels after stenting were also associated with an increased risk of restenosis and that in the large CAPTURE study CRP levels > 10 mg/l were associated with restenosis at 6 months (but not with early events). Surprisingly, in this study the risk of restenosis after PCI was not modified by the use of abciximab, raising doubts on the adequacy of CRP as a guide to therapy in PCI. However all published data, but those of Zhou et al.[25], regarding patients undergoing atherectomy, indicate that CRP is a powerful predictor of late restenosis and that titration before PCI may provide important information. Although no data are yet available on the role of CRP, statins and cholesterol reduction in the prevention of restenosis, it is possible that high doses of statins might be of benefit in reducing the risk of restenosis in patients with high CRP levels. Intriguingly Tomoda and Aoki[26] have observed that high CRP levels (> 3 mg/l) are associated with an increased risk of cardiovascular events, including procedural failure even in primary angioplasty, independently of elevations in the level of markers of myocardial damage.

**Clinical considerations.** Hs-CRP should be measured in all patients undergoing coronary angioplasty for prognostic stratification. Pre-procedural levels are of proved efficacy. On the basis of observations of our group, peak post-procedural and follow-up levels might also be useful, but no data are available to confirm this hypothesis. Whether CRP levels can be used as a guide to therapy in PCI is still unclear. However the very low risk associated with low levels of CRP suggests that in these patients there is no need for provisional stenting or for the use of GP IIb/IIIa.

## C-reactive protein and myocardial infarction

Although no large study has prospectively assessed the value of CRP for the prognostic short- and long-term stratification of patients with ST-segment elevation MI, many data suggest that CRP might be of great value even in this group of patients (Table II)[26-31].

Pietila et al.[27] studied 188 patients with ST-segment elevation MI: the highest serum concentrations of CRP were observed 2 to 4 days after the onset of MI. The mean value of the highest serum concentration of CRP in patients who survived the whole 24-month study period was 65 mg/l. The corresponding values in those who died within 3, 3-6, 6-12 and 12-24 months were 166 (range 139-194), 136 (range 88-184), 85 (range 52-119) and 74 mg/l (range 38-111) respectively. The values in those who died within 3 and 3-6 months of the infarction were significantly different from those in patients who survived the whole period ($p < 0.001$ and $p < 0.05$ respectively). In patients who died of congestive heart failure, the mean highest serum CRP concentration was 226 mg/l (range 189-265).

These data confirm those of a smaller study by Anzai et al.[28], in which post-MI CRP levels > 200 mg/l were associated with an increased risk of cardiac rupture. Intriguingly, in both studies CRP levels, but not creatine kinase levels, were associated with cardiac rupture. The co-localization of CRP and complement[32] in the infarct area and the demonstration, in an animal model, of a larger necrotic area in the presence of both CRP and complement may at least partly explain the association between CRP and cardiac rupture in ST-segment elevation MI.

Tommasi et al.[30] have prospectively studied 64 patients with a low post-MI risk on the basis of their ejection fraction (> 50%) and pre-discharge stress test (no signs of ischemia). Patients with CRP levels > 25.5 mg/l at admission had a 56% recurrence rate for ischemic episodes, infarction and death, with a relative risk of 3.3 compared to the lower quartile (CRP < 4.5 mg/l). The rate of events had already reached 31% in the third quartile (CRP levels > 9.3 mg/l). It is likely that in this group of relatively low risk patients, CRP may be a stronger marker of risk than in high risk patients and this observation may explain negative results such as those of Nikfardjam et al.[31] who retrospectively evaluated a series of 729 unselected patients. However, a significant association between CRP levels and mortality was also observed in a population of old women (mean age 82 years) who, by definition, constitute a high risk group.

An important study was published by Ridker et al.[29]: in this retrospective analysis of the CARE study (post-MI patients randomized to receive pravastatin or placebo), CRP levels in blood samples taken 8 to 9 months after discharge were predictive of future events in a case-control study up to 5 years. The relative risk was 1.77 for patients in the top quintile vs those in the lowest one (CRP levels equal to 6.6 and 1.2 mg/l respectively). More importantly, the risk was attenuated and no longer significant in patients randomized to pravastatin. In a subsequent study[33], a significant reduction in CRP levels was demonstrated in patients randomized to pravastatin, suggesting that this drug, and probably all statins, might have an “anti-inflammatory” effect which does not seem with be associated with the extent of cholesterol reduction.

**Clinical considerations.** Although no large clinical studies designed to assess the prognostic role of CRP in acute ST-segment elevation MI are available, accumulating data suggest that CRP is a useful predictor of the short- (in particular cardiac rupture) and long-term out-

**Table II.** C-reactive protein levels and outcome in myocardial infarction.

| Author | Patients | Primary endpoint | Dosage method | Limit of normal (mg/l) | Results |
|---|---|---|---|---|---|
| Pietila et al.[27], 1996 | 188 pts with acute MI treated with thrombolytic therapy | Total mortality at 3, 3-6, 6-12, 12-24 months after the onset of acute MI (total period: 24 months) | Not better specified immunoassay | No data | Peak CRP levels during 6 days after acute MI in pts who died within 3 and 3-6 months of the acute MI are significantly higher than in those who survived the whole period (166 and 136 vs 65 mg/l, $p < 0.001$ and $p < 0.05$ respectively) |
| Anzai et al.[28], 1997 | 220 pts with acute MI | In-hospital cardiac rupture, cardiac death at 1 year of follow-up | Latex photometric immunoassay | No data | Peak CRP levels during 6 days after acute MI in pts with cardiac rupture were significantly higher than in those without (mean 237 vs 122 mg/l, $p = 0.001$). Peak CRP levels were higher in pts with cardiac deaths than in survivors (260 vs 110 mg/l, $p = 0.006$) |
| Ridker et al.[29], 1998 | 782 pts with previous acute MI (3-20 months before randomization) in a follow-up of 5 years | Cardiac ischemic death, recurrent MI | High sensitivity assay | No data | Pts with events had higher CRP levels on study entry than pts without events (mean 5.6 vs 4.8 mg/l, $p < 0.03$). Quintiles of CRP levels (< 1.2; 1.2-2; 2-3.7; 3.7-6.6; > 6.6): pts with CRP levels in the highest quintile had a RR of recurrent disease 75% higher than those with CRP levels in the lowest one ($p < 0.02$) |
| Tommasi et al.[30], 1999 | 64 pts with acute MI in a follow-up of 13 ± 4 months | Cardiac death, unstable angina, non-fatal reinfarction | Nephelometric | 5 | Pts with events had higher CRP levels on admission than pts without events (mean 36.1 vs 14.8 mg/l). With Cox regression analysis on quartiles of CRP levels (< 4.5; 4.5-9.3; 9.3-25.5; > 25.5), only CRP in the 4th quartile was an independent risk factor for combined endpoint |
| Tomoda and Aoki[26], 2000 | 234 pts with acute MI within 6 hours of onset | In-hospital major cardiac events: acute/subacute coronary reocclusion, reinfarction, target vessel revascularization, death | Latex photometric immunoassay | 3 | The rate of events was significantly higher in pts with CRP levels on admission > 3 mg/l (mean 10.4 mg/l) than in pts with CRP levels < 3 mg/l (mean 1.4 mg/l) (22.4 vs 4.3%, $p < 0.005$). CRP on admission was the sole significant independent predictor of in-hospital events (OR 7.11, $p < 0.005$) |
| Nikfardjam et al.[31], 2000 | 729 pts with acute MI | Total mortality during a follow-up of 3 years | Immuno-turbidimetric assay | No data | With increasing CRP levels on admission (< 0.5; 0.5- < 2; 2- < 5; 5-10; > 10 mg/l) mortality also increased (14, 19, 20, 39, and 28%). After controlling for confounding baseline variables the association between mortality and CRP levels was substantially weakened |

Abbreviations as in table I.

comes in this group of patients. Although it is reasonable to presume that the prognostic value is stronger for relatively low risk patients, there is evidence that CRP levels may constitute a good prognostic marker also in high risk patients. With regard to the best timing of sampling the same considerations made for unstable angina patients hold.

### Stable angina

Medical literature includes various non-specifically addressed studies on the prognostic role of CRP in patients with chronic stable angina. In view of the fact that some of the patients included in the ECAT study were stable, CRP is likely to represent a good prognostic marker even in such cases. The management of non-hospitalized stable angina patients is similar to that recommended for primary prevention.

### Cut-off levels

In daily clinical practice, one of the problems with the use of CRP for the prognostic stratification of patients with ongoing, stable or unstable coronary heart disease is the choice of the cut-off levels for appropriate differentiation of low and high risk patients. As patients with different clinical presentations have been studied using different assays, the data in the literature are not fully comparable. Only a few studies have used the hs-CRP assay in patients with acute coronary syndromes. Because CRP levels in this condition are usually elevated, a hs-CRP assay may not be as crucial as in the field of primary prevention; however, the many data suggesting a very low risk for low levels of CRP even in patients with acute coronary syndromes are in favor of the use of a hs-CRP assay also in these patients.

Data in the literature published to date suggest that it is reasonable to consider two different cut-off levels. Three mg/l is a value to be used for long-term stratification of stable and unstable patients if samples are taken at discharge, and is probably a good marker of the combined short- and long-term endpoint death + MI + new coronary events and of restenosis after a PCI. A CRP level of 10 mg/l can be proposed for the stratification of the risk of death (and to a lesser extent MI). Levels < 3 mg/l are in all studies associated with a low risk of events.

### What to do when C-reactive protein levels are elevated

What are the cut-off levels for CRP? This is the second most frequently answered question in any meeting on CRP. The lack of a specific therapy which has been proved to reduce levels of CRP and risk makes this question quite reasonable. However, the demonstration that statins are particularly effective in the presence of high CRP levels is already a first very clear answer. Patients with high levels of CRP, especially when associated with high or borderline cholesterol levels, should be treated with statins in the long and probably in the short term (in this field, the results of the inflammatory substudy of the MIRACLE trial are awaited). This is also likely to be true, although not yet demonstrated, for patients undergoing a PCI. High CRP levels, associated with a higher risk, suggest a more aggressive medical therapy in the long term, but also, although there are no data to confirm this hypothesis, an aggressive and invasive therapy in the short term, including the use of GP IIb/IIIa inhibitors, high doses of statins, and, when a PCI is necessary, provisional stenting. The use of biochemical markers as a guide to therapy will no longer be a controversial issue in the future and there is no doubt that CRP has all the characteristics to be one of the ideal markers. Whether new therapies, such as IL antagonists or inhibitors of the inflammatory pathway, will be beneficial in the future cannot be anticipated. In this case the role of CRP as a guide to specific therapy would be greatly enhanced.

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