

C-Reactive Protein and Outcomes in Acute Coronary Syndromes: A systematic Review and Meta-Analysis

Luís C. L. Correia e J Pérciles Esteves¹

Escola Bahiana de Medicina, Universidade Federal da Bahia, Salvador, BA – Brasil

Abstract

Despite the association between high-sensitivity C-reactive protein (CRP) and recurrent events in non-ST elevation acute coronary syndromes (ACS), routine determination of this marker has not been recommended.

In order to verify whether the current scientific evidence justifies the inclusion of CRP for risk stratification at hospital admission of patients with ACS, we carried out a systematic review and meta-analysis of the studies indexed in MEDLINE, SciELO or LILACS, with the following inclusion criteria: prospective cohort design and assessment of the prognostic value of CRP, as measured using a high-sensitivity method at the moment of hospital admission of patients with ACS. Nineteen studies met the inclusion criteria.

In relation to the long-term follow-up, there was a consistent association between CRP and cardiovascular events, with an overall odds ratio (OR) of 4.6 (95% CI = 2.3 – 7.6) and overall multivariate OR of 2.5 (95% CI = 1.8-3.4). As for the short-term, nine studies were positive and six were negative, with an overall OR of 1.65 (95% CI = 1.2-2.3). The overall multivariate OR was not obtained for the short-term follow-up, because this measurement was described only in three heterogeneous studies. Only two short-term studies analyzed the incremental predictive value of CRP in relation to multivariate models, with contradicting results.

In conclusion, the small number of assessments of the incremental value of CRP, in conjunction with controversial results regarding the independent predictive value of CRP for short-term events does not support the recommendation of the routine use of CRP for risk stratification at admission of patients with ACS.

Key Words

C-Reactive protein; acute coronary syndrome; prognosis; meta-analysis.

Introduction

In patients with acute coronary syndromes (ACS), atherosclerotic plaque instability is accompanied by exacerbation of inflammation¹. The inflammatory phenomenon hinders plaque stabilization, which theoretically makes these patients more vulnerable to recurrent coronary events². This vascular process is widespread, not limited to the site of plaque rupture; it affects the whole coronary bed, and, at the systemic level, may be detected by determining plasma inflammatory markers³. This is the mechanistic rationale for the prognostic value of inflammatory markers in patients with acute coronary syndromes. Among the inflammatory markers, C-reactive protein is the one that has been more frequently studied by means of high sensitivity methods⁴.

Throughout the past 15 years, several publications have indicated that C-reactive protein levels have an independent predictive value for recurrent coronary events in patients with non-ST elevation ACS⁵. However, this approach has not been adopted in clinical practice, nor has the recommendation for the determination of this marker been incorporated to Brazilian⁶, American^{5,7} or European⁸ guidelines. Thus, the objective of this systematic review was to evaluate whether the current evidence justifies the inclusion of C-reactive protein for risk stratification at hospital admission of patients with non-ST elevation ACS.

Methods

Literature Research

The MEDLINE (Medical Literature Analysis and Retrieval System) database was the main source used for the systematic review of the articles on the subject studied. To investigate studies not indexed in MEDLINE and carried out in Latin America, the SciELO (Scientific Electronic Library Online) and LILACS (Literatura Latino-Americana e do Caribe em Ciências de Saúde) databases were used by applying the same key words used in MEDLINE. The references of each original article and review articles were checked in order to select studies that had not been identified by the research in the databases.

Initially, the MeSH (Medical Subject Headings) vocabulary was used for the definition of the terms for research in the titles of the studies. The term C-reactive

Mailing Address: Luís C. L. Correia •

Av. Princesa Leopoldina 19/402 – Graça – 40150080 – Salvador, BA – Brasil
E-mail: lccorreia@cardiol.br, lccorreia@terra.com.br
Artigo recebido em 11/01/10; revisado recebido em 14/04/10;
aceito em 17/05/10.

protein was chosen for combination with the terms acute coronary syndromes, myocardial infarction, and unstable angina, resulting in a total of three combinations of two terms connected by the preposition AND. After reading of the titles and summaries retrieved, the studies with the following characteristics were selected: prospective cohort design of patients with non-ST elevation ACS, and assessment of the prognostic value of C-reactive protein, as measured by a high-sensitivity method at the moment of hospital admission.

Studies with evident methodological biases were excluded.

Outcome measures

The following outcome measures were considered: death or composite cardiovascular events. There were different definitions of composite outcome measures in the studies: cardiovascular death and infarction or cardiovascular death, infarction and recurrent angina. These studies were analyzed together, with any of the combinations been considered as cardiovascular events. Outcome measures in the short-term follow-up were defined as occurring during hospitalization or within 30 days at most. Outcome measures in long-term follow-up were defined as those occurring after at least three months of follow-up.

Data analysis

Initially, the characteristics of the different studies were presented in the form of tables. Studies analyzing events in the short-term follow-up (≤ 30 days) and those analyzing events in the long-term follow-up (≥ 3 months) were described separately. Some analyzed both outcome measures, and are therefore shown in both tables.

In the univariate analysis, studies reporting the absolute incidence of events according to a cut-off point of C-reactive protein were combined. Studies limited to the assessment of C-reactive protein as a continuous variable were not included in the meta-analysis. Initially, the results of the different studies were compared using the Cochrane Q statistic, with $p < 0.05$ indicating heterogeneity. When heterogeneity was present, the studies were combined by the random effects model (DerSimonian and Laird method). Otherwise, the fixed effects model was used (Mantel-Haenszel method).

The composite results were expressed as odds ratio (OR) and 95% confidence interval (CI). Also, summary ROC (sROC) curves were obtained with description of the summary C-statistic (area under the curve) and respective 95% CI. The “threshold effect” of the cut-off point of C-reactive protein was evaluated in each study using the

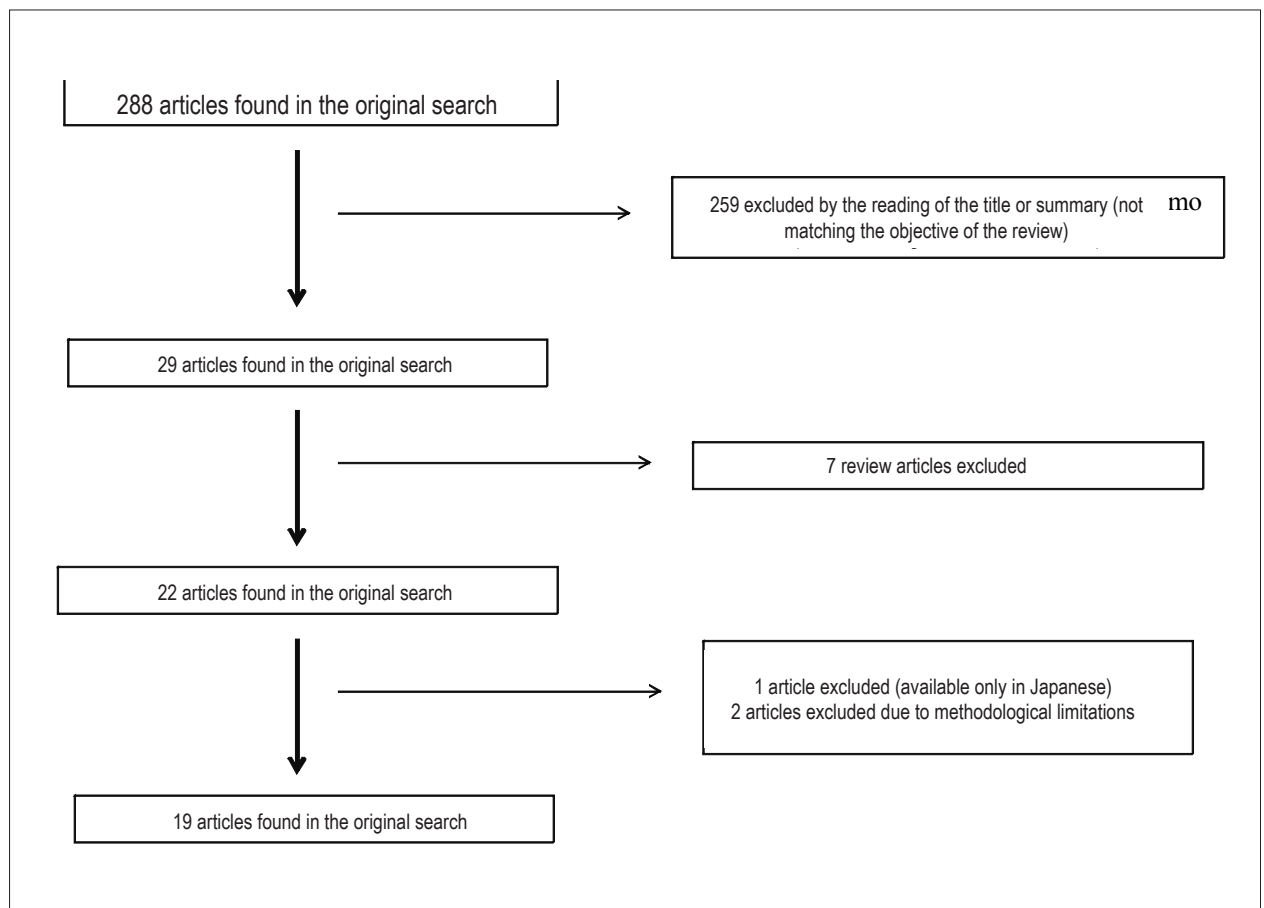


Figure 1 - Schematic representation of the study selection for systematic review.

Spearman correlation between sensitivity and specificity. For the analysis of sensitivity, the influences of methodological differences on the results of the meta-analysis were tested together using meta-regression analysis.

In order to carry out a joint analysis of data from multivariate analyses, the OR described in each study were combined. Studies describing the multivariate analysis by relative risk or hazard ratio were not combined. The Meta-DiSc software, version 1.4 (*Universidad Complutense, Madrid, Spain*)⁹ was used for the statistical analysis, except for the combination of odds ratios, when the Comprehensive Meta-Analysis, version 2 (Biostat, Inc, Englewood, NJ, USA)¹⁰ was used.

Results

Study selection

The research on articles published up to May 2009 resulted in 288 studies, of which 259 were excluded by the reading of the title, which indicated that the studies were not related to the assessment of the prognostic value of C-reactive protein in patients with non-ST elevation ACS. Of the remaining 29 studies, 7 were excluded for being review articles and one for being published in a Japanese journal, with full version available only in Japanese¹¹. Other two articles were excluded due to methodological problems: a Japanese study, which evaluated only C-reactive protein combined with serum amyloid A¹²; and a Chilean study which only addressed C-reactive protein as a continuous variable and, in the multivariate model, included only three biomarkers without adjustment for the clinical variables¹³.

Thus, 19 studies were included in this systematic review (Figure 1).

Characteristics of the studies

Nineteen studies were selected; 15 were carried out by North American or European groups^{1,14-27}, three by Brazilian groups²⁸⁻³⁰ and one by an Argentinean group³¹. All these studies were published in journals with an impact factor ≥ 3 , except for two Brazilian studies^{28,29}. The first one dates back to 1994; it was conducted by Liuzzo et al¹⁴ and published in the *New England Journal of Medicine*. Despite the small sample size of only 32 patients with unstable angina, the impact of this study stems from its original idea of predicting cardiovascular events based on the inflammatory status of patients with ACS. The demonstration that C-reactive protein levels predicted in-hospital events served as the basis for the performance of other 18 studies which started to be published successively as of three years later.

The population samples of these studies consisted predominantly of patients with non-ST elevation ACS and six studies also included ST-elevation myocardial infarction^{21,23-26,28}. The sample size of the studies increased throughout the years, ranging from 32 to 7,108 patients (mean of $1,123 \pm 1,674$); seven studies had more than 1,000 patients^{20,21,23-27}, in a total of 21,339 patients studied. C-reactive protein was measured in all studies by means of a high-sensitivity method; 11 used nephelometry^{14-19,21-24,26,28-30}, three used turbidimetry^{1,25,27}, one used luminometry²⁰, and two used ELISA (Enzyme Linked Immunosorbent Assay)³¹.

Thus, we can conclude that there is a significant number of studies and patients studied with adequate technique of plasma C-reactive protein determination.

C-reactive protein: long-term prediction of events

Eight studies evaluated the prognostic value of C-reactive protein in relation to recurrent events in a follow-up of at least

Table 1 - Characteristics of the studies analyzing the predictive value of C-reactive protein in the long term

Author	Year	N	Population	Follow-up	Outcome measures	Cut-off point	Outcome measures PCR \uparrow vs. PCR \downarrow	Independent Association	Incremental Value
Winter	1999	150	SCASS	6 months	Death, AMI, UA	5 mg/L (Arbitrary)	23.0% vs. 1.0% *	Yes (OR not reported)	Not Analyzed
Ferreirós	1999	199	AI	3 months	Death, AMI, AR	15 mg/L (ROC)	77.0% vs. 13.0% *	Not Analyzed	Not Analyzed
Lindahl	2000	917	SCASS	3 years	Death	10 mg/L (Arbitrary)	17.0% vs. 6.7% *	RR = 2.6 (1.5–4.5)	Not Analyzed
Heeschen	2000	447	AI	6 months	Death, AMI	10 mg/L (ROC)	19.0% vs. 5.4% *	OR = 1.97 (1.2–3.6)	Not Analyzed
Mueller	2002	1.042	SCASS	2 years	Death	10 mg/L (Arbitrary)	13.0% vs. 3.9% *	OR = 4.07 (2.3–7.3)	Not Analyzed
Bodi ²²	2005	515	SCASS	6 months	Death, AMI	11 mg/L (ROC)	23.0% vs. 8.9% *	OR = 2.1 (1.2–3.8)	Not Analyzed
Scirica	2007	3.225	SCA	10 months	Death	9 mg/L (ROC)	Association Present Non Dichotomous	HR = 2.2 (1.6–3.0)	Not Analyzed
Bogaty	2008	1.210	SCA	1 year	Death, AMI, UA	Continuous	Association Present Non Dichotomous	Association Absent Non Dichotomous	Not Analyzed

N: sample size; Cut-off point: in parenthesis, the method used to choose the reference value – whether using the best point in the ROC curve or arbitrarily;

CRP \uparrow : C-reactive protein above the cut-off point; CRP \downarrow : C-reactive protein below the cut-off point.

* Statistically significant difference of outcome measures between patients with and without increased C-reactive protein; OR: odds ratio; RR: relative risk; HR: hazard ratio.

ACS: ST-elevation and non-ST elevation acute coronary syndromes; NSTEMI: non-ST elevation acute coronary syndromes;

UA: unstable angina; AMI: acute myocardial infarction

three months, with mean follow-up of 13 ± 11 months. All showed a significant association between C-reactive protein and cardiovascular events^{1,18,19,22-24,27,31} (Table 1).

As for the meta-analytic grouping of the study results, Bogady et al²³ and Scirica et al²⁴ studies were not included because C-reactive protein was analyzed as a numerical variable, and they did not describe the incidences of events according to the subgroups of CRP investigation. Thus, the long-term results of six studies were combined. In all these studies, there was a positive and statistically significant association between C-reactive protein and outcome measures; however, the analysis of heterogeneity showed a quantitative difference ($p = 0.007$), i.e., in relation to the magnitude of the association. The combination of studies using the random model resulted in an OR of 4.6 (95% CI = 2.3 – 7.6) (Figure 2). The sROC curve showed a C-statistic of 0.75 (95% CI = 0.65 – 0.85) (Figure 3).

Analysis of sensitivity of the prediction of long-term events

Two characteristics varied significantly among the studies of this meta-analysis. First, the form of determination of the cut-off point for C-reactive protein: three studies identified the cut-off point by using the ROC curve and found 15 mg/L³¹, 10 mg/L¹⁹, and 11 mg/L²², respectively. The other three studies arbitrarily chose the cut-off points of 5 mg/L¹⁸, 10 mg/L¹ and 10 mg/L²⁷, respectively. According to the meta-regression analysis, there was no influence of the form of determination of the cut-off points on the results of the studies (OR = 0.1; 95% CI = 0 – 36; $p = 0.23$). Also, there was no linear association between sensitivity and specificity ($p = 0.40$), thus indicating absence of influence of the cut-off point values on the results of the studies (threshold effect).

The second characteristic that differed among the studies was the definition of outcome measures, with two meta-

Table 2 - Characteristics of the studies that evaluated the predictive value of C-reactive protein in the short term

Author	Year	N	Population	Follow-up	Outcome measures	Cut-off point	Outcome measures PCR ↑ vs. PCR ↓	Independent Association	Incremental Value
Liuzzo	1994	32	UA	In-hospital	AMI, Angina	(arbitrary)	23% vs. 0%	Not Analyzed	Not Analyzed
Oltrona	1997	140	UA	In-hospital	AMI, Angina	(arbitrary)	25% vs. 22%	Not Analyzed	Not Analyzed
Benamer	1998	195	UA	In-hospital	Death, AMI, Angina	(arbitrary)	11% vs. 21%	Association absent OR not described	Not Analyzed
Morrow	1998	437	NSTEACS	In-hospital	Death	(arbitrary)	5,2% vs. 0,3%*	Not Analyzed	Not Analyzed
Ferreirós	1999	199	UA	In-hospital	Death, AMI, Angina	(ROC)	12% vs. 14%	Association absent OR not described	Not Analyzed
Heeschen	2000	447	UA	In-hospital	Death, AMI	(ROC)	2,2% vs. 2,6%	Not Analyzed	Not Analyzed
Mueller	2002	1.042	NSTEACS	In-hospital	Death	(arbitrary)	3,6% vs. 1,0%*	Not Analyzed	Not Analyzed
James	2003	7.108	NSTEACS	In-hospital	Death, AMI	(arbitrary)	9,5 vs. 7,0%*	OR = 1,07 (0,87 - 1,3)	Not Analyzed
Oltrona	2004	1.773	ACS	30 days	Death, AMI	(arbitrary)	Association present Percentages not described	RR = 1,43 (0,99 - 2,1)	No incremental value
Duarte	2005	199	ACS	In-hospital	Death, AMI, Angina, CHF	Continuous	Association present Non dichotomous	Association absent OR not described	Not Analyzed
Foussas	2005	1.846	ACS	In-hospital	Death, AMI, Angina	(ROC)	23% vs. 15%*	HR = 1,8 (1,5 - 2,6)	Not Analyzed
Manenti	2006	172	NSTEACS	30 days	Death, Reinfarction	(arbitrary)	21% vs. 18%	Association absent OR not described	Not Analyzed
Correia	2007	86	NSTEACS	In-hospital	Death, AMI	(ROC)	20% vs. 1,7%*	OR = 14 (1,6 - 121)	With incremental value
Scirica	2007	3.225	ACS	30 days	Death	(ROC)	Association Present Percentages not described	HR = 2,3 (1,5 - 3,6)	Not Analyzed
Kuch	2008	1.646	AMI	In-hospital	Death	(arbitrary)	12% vs. 6,4%*	OR = 4,6 (1,9 - 13)	Not Analyzed

N: sample size; Cut-off point: in parenthesis, the method use to choose the reference value – whether using the best point in the ROC curve or arbitrarily; CRP ↑: C-reactive protein above the cut-off point; CRP ↓: C-reactive protein below the cut-off point.

* Statistically significant difference of endpoints between patients with and without increased C-reactive protein; OR: odds ratio; RR: relative risk; HR: hazard ratio.

ACS: ST-elevation and non-ST elevation acute coronary syndromes; NSTEACS: non-ST elevation acute coronary syndromes;

UA: unstable angina; AMI: acute myocardial infarction

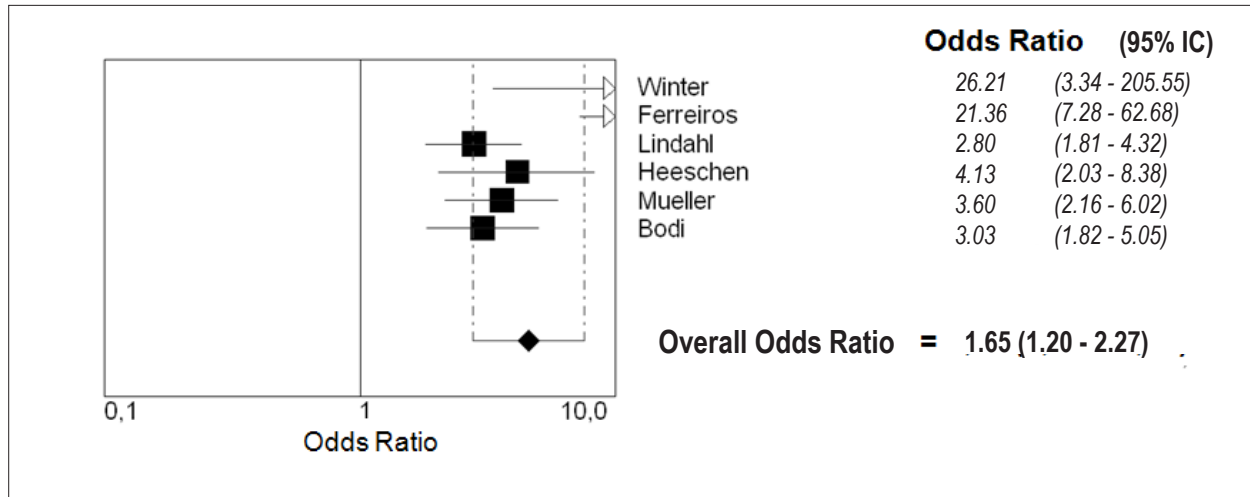


Figure 2 - Overall representation and individual representation of each study in relation to the association of high levels of C-reactive protein with cardiovascular events in the long-term follow-up: OR (odds ratio) and 95% CI (confidence intervals)

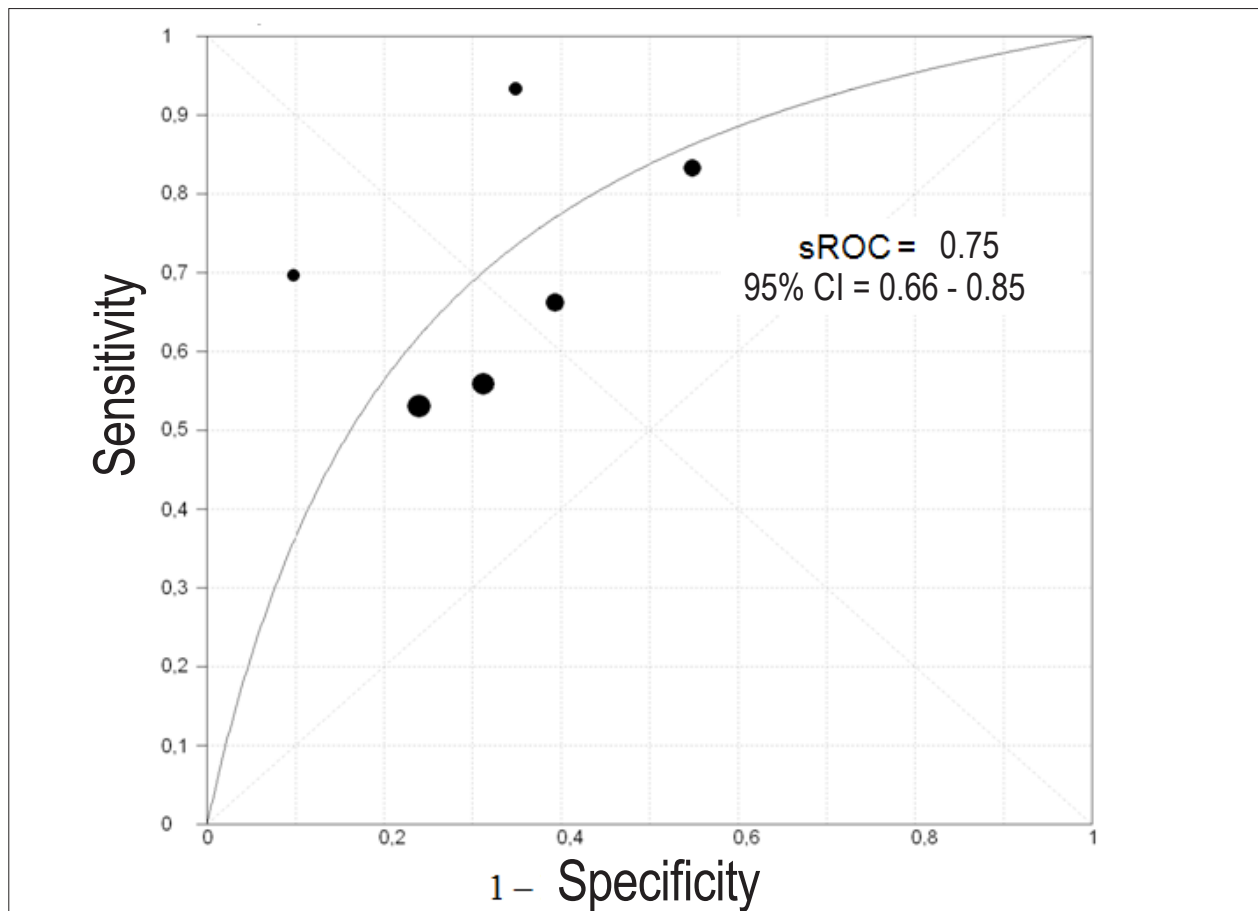


Figure 3 - Summary ROC curve of the association of the different cut-off points of C-reactive protein with cardiovascular events in the long-term follow-up. CI: confidence interval.

analysis studies analyzing death alone^{1,27} and four analyzing composite outcome measures^{18,19,22,31}. Likewise, the meta-regression analysis did not show any influence of the type of outcome measure on the results (OR = 0.35; 95% CI = 0.02 – 4.5; $p = 0.27$).

C-reactive protein: short-term prediction of events

Fifteen studies analyzed the prediction of events up to 30 days^{14-17,19-21,25-31}. Unlike for the long-term follow-up, the results of the studies were conflicting: nine studies were positive^{14,17,20,21,25-27,30} and six were negative^{15,16,19,28,29,31} (Table 2). On average, the group of positive studies had larger sample sizes ($1,911 \pm 2,197$ patients), with six of the seven studies with more than 1,000 patients. On the other hand, the group of negative studies had a mean sample size of 225 ± 110 patients, the larger of which with 447 individuals. This suggests that the negative results of these studies may have been due to the reduced statistical power.

Meta-analytic approach was used with the 12 studies which compared the incidence of events between two dichotomous groups according to the level of C-reactive protein^{14-17,19,20,25-27,29-31}. Duarte et al's study²⁸ was not included in this analysis because it assessed C-reactive protein as a continuous variable. One of Oltrona et al's study²¹ and Scirica et al's study²⁴ were not included in the meta-analysis because they expressed their results only as relative risk, and did not provide the absolute incidence of events. The meta-analysis showed significant heterogeneity among the studies ($p = 0.002$); for this reason, the OR was calculated using the random effects model, which resulted in 1.65 (95% CI = 1.20 – 2.27), thus confirming prediction of in-hospital events (Figure 4). The sROC curve showed a C-statistic of 0.57 (95% CI = 0.54 - 0.60) (Figure 5).

Analysis of sensitivity: short-term prediction of events

Three characteristics were significantly different among the studies. First, the form of determination of the cut-off point for C-reactive protein: four studies identified the cut-off point by using the ROC curve^{19,26,30,31} and other eight studies chose the cut-off point arbitrarily^{14-17,20,25,27,29}. According to the meta-regression analysis, the form of determination of the cut-off point had no influence on the study results (OR = 1.34; 95% CI = 0.52 – 3.47; $p = 0.49$). Also, there was no linear association between sensitivity and specificity ($p = 0.55$), thus indicating absence of influence of cut-off values on the study results.

The second difference among the studies was the definition of outcome measures, with three studies of the meta-analysis evaluating death alone^{17,25,27} and the other nine studies evaluating composite outcome measures^{14-16,19,20,26,29-31}. Likewise, the meta-regression analysis did not show influence of the type of outcome measure on the results (OR = 0.35; 95% CI = 0.02 – 4.5; $p = 0.27$).

Finally, ST-elevation myocardial infarction was included in two studies^{25,26}, whereas the other 10 analyzed only non-ST elevation ACS. This did not influence the results either (OR = 0.70; 95% CI = 0.36 – 1.35; $p = 0.25$) (Table 3).

Independent predictive value of C-reactive protein

Most of the studies, except for the three initial ones^{14,15,17}, adjusted the predictive value of C-reactive protein to the clinical and laboratory variables. In five studies, important covariables were left out of the statistical model^{16,18,25,28,32}, whereas in other 11 studies the multivariate analysis was adequate^{1,19-24,26,27,31}. Foussas et al's²⁶ and Correia et al's³⁰

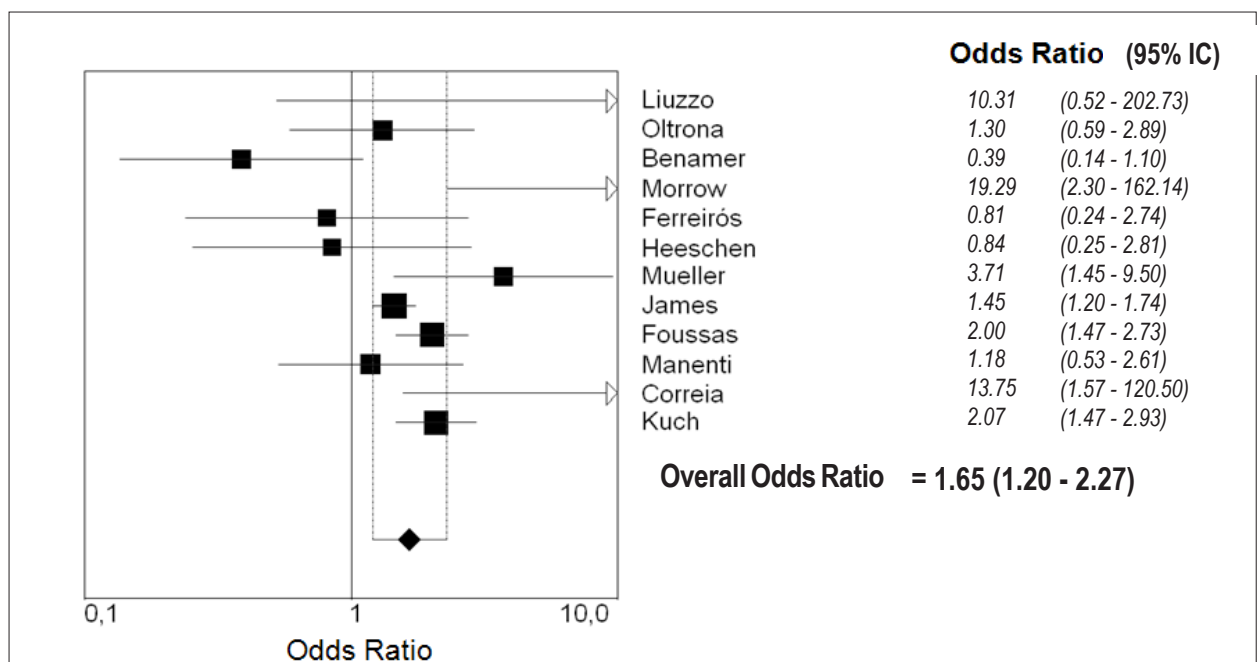


Figure 4 - Overall representation and individual representation of each study in relation to the association of high levels of C-reactive protein with cardiovascular events in the short-term follow-up: OR (odds ratio) and 95% CI (confidence intervals).

Table 3 - Analysis of sensitivity using meta-regression of subgroups regarding the short-term prognostic value of C-reactive protein

	Odds ratio	95% CI	p value
Use of ROC curve	1.34	0.52 – 3.5	0.49
Only Non-ST elevation ACS	0.70	0.36 – 1.35	0.25
Death as the only Outcome Measure	1.31	0.80 – 2.16	0.24

Use of the ROC curve to determine the cut-off point, instead of arbitrary choice.

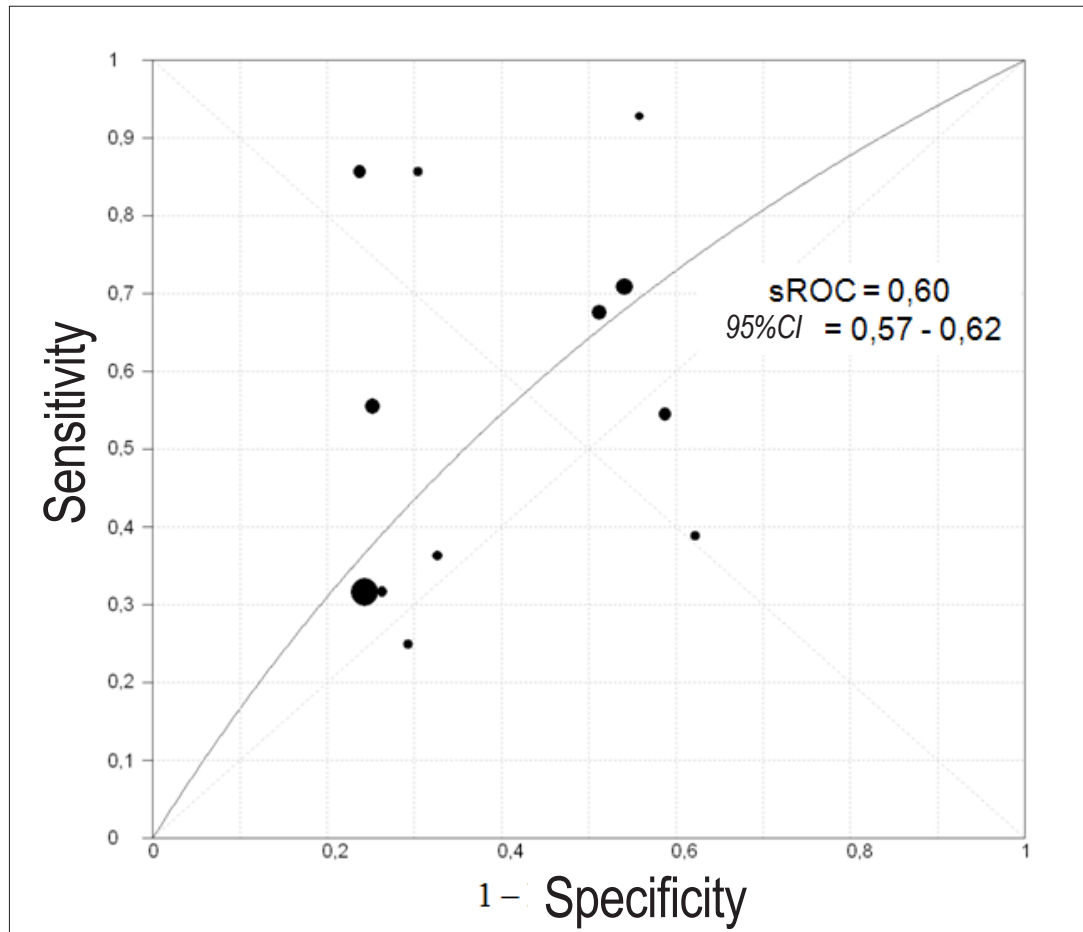


Figura 5 - Summary ROC curve of the association of the different cut-off points of C-reactive protein with cardiovascular events in the short-term follow-up. CI: confidence interval.

studies should be particularly pointed out for being the only ones to adjust the level of C-reactive protein to a validated risk score, the TIMI risk score.

Of the eight studies which evaluated the long-term prognostic value of CRP, six confirmed its independent predictive value by using the multivariate analysis^{1,18,19,22,24,27}, and one did not carry out this analysis³¹. On the other hand, the recent Bogaty et al²³ on a cohort of 1,210 patients with ACS found no multivariate association of C-reactive protein with long-term recurrent events; this study was worthy of attention for its negative result²³. Because of the unprecedented finding of the absence of an independent predictive value, this study is worthy of a detailed discussion.

First, the analysis of methodological issues did not show superiority of Bogaty et al²³ in relation to the other studies. Second, it has been demonstrated that the predictive value of C-reactive protein in patients with unstable angina or non-ST elevation myocardial infarction is greater than its predictive ability in ST-elevation myocardial infarction, where the higher degree of necrosis influences C-reactive protein levels²⁵. Thus, the fact that 30.0% of the patients presented with ST-elevation myocardial infarction may have contributed to the negative result of Bogaty et al²³. Third, that study showed significant predictive ability of C-reactive protein in the univariate analysis, but not in the multivariate analysis. Unlike in the

other studies, the level of C-reactive protein was included as a continuous variable in the logistic regression, and this reduces its prediction strength because it is evaluated together with other categorical variables. This may have been the main reason for the negative result of Bogaty et al²³.

Five long-term studies reported measures of association from the multivariate analysis. Three of them used OR, thus permitting data combination. These three studies showed homogeneity ($p = 0.14$), and the fixed effects model resulted in $OR = 2.5$ (95% CI = 1.8 – 3.4).

In relation to the independent predictive value of C-reactive protein for short-term events, 10 studies carried out a multivariate analysis and only four indicated an independent predictive value, thus showing controversial findings. Only three studies described multivariate OR and, due to the heterogeneous of their results, we chose not to combine them, to avoid a high potential of selection bias in such analysis.

Incremental value of C-reactive protein

Of the 19 articles selected, only two quantified the incremental value of C-reactive protein, both in relation to the short-term predictive value. In the first, Oltrona et al¹⁵ found that the inclusion of C-reactive protein in the logistic regression model did not add to the C-statistic. Oltrona et al¹⁵ has a large sample size ($N = 1,773$) and the advantage of including a large number of covariables²¹. On the other hand, Oltrona et al¹⁵ study has the disadvantage of also including ST-elevation myocardial infarction, which theoretically reduces the predictive value of C-reactive protein. Although statistically correct, Oltrona et al¹⁵ approach to how much C-reactive protein adds to a predictive model derived from the study sample itself makes it more difficult to find an additional predictive value of a biomarker. This occurs because the multivariate predictive model is optimized since it was derived from the population itself.

In the second study, Correia et al³⁰ specifically selected patients with non-ST elevation ACS and analyzed the incremental value in relation to a validated risk score, the TIMI risk score. Despite its small sample size, after inclusion of the information on C-reactive protein this study showed an increment in TIMI's C-statistic by 0.06³⁰.

Discussion

The objective of the present systematic review was to evaluate whether there are evidences corroborating the use of C-reactive protein as a risk predictor at admission of patients with non-ST elevation ACS. The prognostic value of this marker has been evaluated in the short term (in-hospital or 30 days) and long term (> three months).

We observed that, in the long-term, evidences showing association between C-reactive protein and the incidence of outcome measures are consistent in both univariate and multivariate analyses. On the other hand, the short-term results are qualitatively heterogeneous, i.e., some indicate the absence of association and others suggest an association between C-reactive protein and outcome measures. In the present meta-analysis, the mean effect of short-term studies

shows a univariate association between C-reactive protein and cardiovascular risk³². However, the multivariate analyses of these studies are contradictory and the results could not be combined because the minority of them provided the multivariate odds ratio. Thus, the present analysis shows a long-term prognostic value and indicates controversy regarding the short-term prognostic value.

Although the independent risk prediction is a necessary condition in the validation of a new marker, it does not suffice. Interrupting the evaluation of the predictor in this phase, and considering it validated for clinical use is a common mistake. Not all independent predictors add to the prognostic accuracy of the classical prediction models in a clinically relevant fashion³³. This brings up an important question: does the novel risk marker provide an incremental utility to the models applied in clinical practice? The answer should be obtained by comparing the performance of a predictive model including usual variables with that of an alternative model resulting from the incorporation of the novel marker to the classical model. That is, when a new variable is included in a risk score, how much does the performance of this score improve? The most common way of addressing this question is by measuring the increment in C-statistic after incorporation of the novel biomarker³⁴.

In the present review, only two studies addressed this issue with conflicting results, one negative²¹ and the other positive³⁰. Although Correia et al³⁰, whose results were positive, had the methodological advantages reported in the results of the present systematic review, the negative Oltrona et al²¹ has a sample size 20 times larger than that of the former, so that their results should also be valued. Therefore, there are no conclusive evidences regarding the incremental value (clinical utility) of C-reactive protein in relation to the usual risk prediction.

Given the lack of studies on the incremental value of C-reactive protein, we can deduct that it is present based on the strength of association between C-reactive protein and the outcome measures. It has been reported that, in order to add to the C-statistic (> 0.05) in a clinically relevant fashion, a marker usually requires an odds ratio > 3 ³⁵. In the present analysis, the composite odds ratio of 4.6 for the long term seems a favorable number. However, this is the univariate odds ratio, probably overestimated in relation to the multivariate value. Also, the lower limit of the confidence interval is 2.3, and this raises doubt as to the incremental value. Even more uncertain is the short-term incremental value, because the odds ratio of the meta-analysis was 1.6, thus suggesting absence of an incremental value of C-reactive protein.

We should point out that the reasoning exposed is inferential, and the ultimate answer to this question will come with further analyses on the incremental value, which can be carried out in the very databases of the studies published. The importance of this type of analysis is exemplified by the issue of C-reactive protein as a risk predictor in apparently healthy individuals. In this case, C-reactive protein determination does not add to the C-statistic of the Framingham score, although it has an independent association with cardiovascular events³⁶.

The methodological differences of the studies analyzed represent potential biases in the results of this systematic review. For instance, there is a wide variation among the studies regarding the cut-off points, types of outcome measures used, and target populations. However, the analyses of sensitivity indicated that these characteristics did not influence the results of the meta-analysis. Another limitation is the absence of information concerning the odds ratio of most of the studies, and this prevented them from being correctly combined as regards the analysis of the independent predictive value (multivariate analysis).

The stand of current guidelines on non-ST elevation ACS is not clear in relation to the use of C-reactive protein. The Brazilian guideline does not even mention inflammatory markers, whereas the American and European guidelines describe the studies which show the association between C-reactive protein and outcome, although not conclusively from the point of view of recommendation.

Therefore, the present systematic review fills this gap with the following conclusion: despite the consistent association between

the C-reactive protein level at admission and the long-term outcome of patients with ACS, the lack of definitive information regarding its incremental prognostic value does not permit the recommendation of the routine determination of this biomarker in patients with non-ST elevation ACS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of free teaching of Louis C. L. Correia Federal University of Bahia.

References

1. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. *N Engl J Med.* 2000; 343 (16): 1139-47.
2. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation.* 2002; 105 (9): 1135-43.
3. Buffon A, Biasucci LM, Liuzzo G, D'Onofrio G, Crea F, Maseri A. Widespread coronary inflammation in unstable angina. *N Engl J Med.* 2002; 347 (1): 5-12.
4. Rifai N, Tracy RP, Ridker PM. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. *Clin Chem.* 1999; 45 (12): 2136-41.
5. Morrow DA, Cannon CP, Jesse RL, Newby LK, Ravkilde J, Storrow AB, et al; NACB WRITING GROUP. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical Characteristics and Utilization of Biochemical Markers in Acute Coronary Syndromes. *Circulation.* 2007; 115 (13): e356-e375.
6. Nicolau JC, Timerman A, Piegas LS, Marin Neto JA, Rassi A Jr. Guidelines for unstable angina and non-ST-segment elevation myocardial infarction of the Brazilian Society of Cardiology (II Edition, 2007). *Arq Bras Cardiol.* 2007; 89 (4): e89-e131.
7. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DEJ, et al. ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) Developed in Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol.* 2007; 50 (7): e1-e157.
8. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. *Eur Heart J.* 2007; 28 (13): 1598-660.
9. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol.* 2006; 6: 31.
10. Bax L, Yu LM, Ikeda N, Moons KG. A systematic comparison of software dedicated to meta-analysis of causal studies. *BMC Med Res Methodol.* 2007; 7: 40.
11. Tanaka H, Tsurumi Y, Kasanuki H. Prognostic value of C-reactive protein and troponin T level in patients with unstable angina pectoris. *J Cardiol.* 2006; 47 (4): 173-9.
12. Kosuge M, Ebina T, Ishikawa T, Hibi K, Tsukahara K, Okuda J, et al. Serum amyloid A is a better predictor of clinical outcomes than C-reactive protein in non-ST-segment elevation acute coronary syndromes. *Circ J.* 2007; 71 (2): 186-90.
13. Baeza VR, Corbalan HR, Castro GP, Acevedo BM, Quiroga GT, Viviani GP. Coronary biomarkers and long-term clinical outcome in acute coronary syndrome without ST segment elevation. *Rev Med Chil.* 2005; 133 (11): 1285-93.
14. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, et al. The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N Engl J Med.* 1994; 331 (7): 417-24.
15. Oltrona L, Ardissino D, Merlini PA, Spinola A, Chiodo F, Pezzano A. C-reactive protein elevation and early outcome in patients with unstable angina pectoris. *Am J Cardiol.* 1997; 80 (8): 1002-6.
16. Benamer H, Steg PG, Benessiano J, Vicaut E, Gaultier CJ, Boccard A, et al. Comparison of the prognostic value of C-reactive protein and troponin I in patients with unstable angina pectoris. *Am J Cardiol.* 1998; 82 (7): 845-50.
17. Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. *Thrombolysis in Myocardial Infarction.* *J Am Coll Cardiol.* 1998; 31 (7): 1460-5.
18. de Winter RJ, Bholasingh R, Lijmer JG, Koster RW, Gorgels JP, Schouten Y, et al. Independent prognostic value of C-reactive protein and troponin I in patients with unstable angina or non-Q-wave myocardial infarction. *Cardiovasc Res.* 1999; 42 (1): 240-5.
19. Heeschen C, Hamm CW, Bruemmer J, Simoons ML. Predictive value of C-reactive protein and troponin T in patients with unstable angina: a

- comparative analysis. CAPTURE Investigators. Chimeric c7E3 AntiPlatelet Therapy in Unstable angina Refractory to standard treatment trial. *J Am Coll Cardiol.* 2000; 35 (6): 1535-42.
20. James SK, Armstrong P, Barnathan E, Califf R, Lindahl B, Siegbahn A, et al. Troponin and C-reactive protein have different relations to subsequent mortality and myocardial infarction after acute coronary syndrome: a GUSTO-IV substudy. *J Am Coll Cardiol.* 2003; 41 (6): 916-24.
 21. Oltrona L, Ottani F, Galvani M. Clinical significance of a single measurement of troponin-I and C-reactive protein at admission in 1773 consecutive patients with acute coronary syndromes. *Am Heart J.* 2004; 148 (3): 405-15.
 22. Bodi V, Sanchis J, Llacer A, Facila L, Nunez J, Bertomeu V, et al. Risk stratification in non-ST elevation acute coronary syndromes: predictive power of troponin I, C-reactive protein, fibrinogen and homocysteine. *Int J Cardiol.* 2005; 98 (2): 277-83.
 23. Bogaty P, Boyer L, Simard S, Dauwe F, Dupuis R, Verret B, et al. Clinical utility of C-reactive protein measured at admission, hospital discharge, and 1 month later to predict outcome in patients with acute coronary disease. The RISCA (recurrence and inflammation in the acute coronary syndromes) study. *J Am Coll Cardiol.* 2008; 51 (24): 2339-46.
 24. Scirica BM, Morrow DA, Cannon CP, de Lemos JA, Murphy S, Sabatine MS, et al. Clinical application of C-reactive protein across the spectrum of acute coronary syndromes. *Clin Chem.* 2007; 53 (1): 1800-7.
 25. Kuch B, von Scheidt W, Kling B, Heier M, Hoermann A, Meisinger C. Differential impact of admission C-reactive protein levels on 28-day mortality risk in patients with ST-elevation versus non-ST-elevation myocardial infarction (from the Monitoring Trends and Determinants on Cardiovascular Diseases [MONICA]/Cooperative Health Research in the Region of Augsburg [KORA] Augsburg Myocardial Infarction Registry). *Am J Cardiol.* 2008; 102 (9): 1125-30.
 26. Foussas SG, Zairis MN, Lyras AG, Patsourakos NG, Tsimpiris VG, Katsaros K, et al. Early prognostic usefulness of C-reactive protein added to the Thrombolysis In Myocardial Infarction risk score in acute coronary syndromes. *Am J Cardiol.* 2005; 96 (4): 533-7.
 27. Mueller C, Buettner HJ, Hodgson JM, Marsch S, Perruchoud AP, Roskamm H, et al. Inflammation and long-term mortality after Non-ST elevation acute coronary syndrome treated with a very early invasive strategy in 1042 consecutive patients. *Circulation.* 2002; 105 (12): 1412-5.
 28. Duarte ER, Pellanda LC, Portal VL. Inflammatory, lipid, and metabolic profile in acute ischemic syndrome: correlation with hospital and posthospital events. *Arq Bras Cardiol.* 2005; 84 (2): 122-9.
 29. Manenti ER, Bodanese LC, Camey SA, Polanczyk CA. Prognostic value of serum biomarkers in association with TIMI risk score for acute coronary syndromes. *Clin Cardiol.* 2006; 29 (9): 405-10.
 30. Correia LC, Lima JC, Rocha MS, D'Oliveira JA, Pericles EJ. Does high-sensitivity C-reactive protein add prognostic value to the TIMI-Risk Score in individuals with non-ST elevation acute coronary syndromes? *Clin Chim Acta.* 2007; 375 (1-2): 124-8.
 31. Ferreiros ER, Boissonnet CP, Pizarro R, Merletti PF, Corrado G, Cagide A, et al. Independent prognostic value of elevated C-reactive protein in unstable angina. *Circulation.* 1999; 100 (19): 1958-63.
 32. Biasucci LM, Liuzzo G, Grillo RL, Caligiuri G, Rebuzzi AG, Buffon A, et al. Elevated levels of C-reactive protein at discharge in patients with unstable angina predict recurrent instability. *Circulation.* 1999; 99 (7): 855-60.
 33. O'Donoghue M, Morrow DA. The future of biomarkers in the management of patients with acute coronary syndromes. *Curr Opin Cardiol.* 2008; 23 (4): 309-14.
 34. Wilson PW. Challenges to improve coronary heart disease risk assessment. *JAMA.* 2009; 302 (21): 2369-70.
 35. Lloyd-Jones DM, Liu K, Tian L, Greenland P. Narrative review: assessment of C-reactive protein in risk prediction for cardiovascular disease. *Ann Intern Med.* 2006; 145 (1): 35-42.
 36. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med.* 2006; 355 (25): 2631-9.