

Prognostic value of pre-discharge exercise testing and serum C-reactive protein in patients with unstable angina

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Exercise test;
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Background. Both exercise testing and C-reactive protein (CRP) serum levels have been shown to predict clinical events in patients with unstable angina. However, no previous study carefully compared their relative prognostic value in this clinical setting.

Methods. We reviewed data of 96 consecutive patients with unstable angina (77 males, 19 females, mean age 63.1 ± 9.5 years), who were free from clinical events during hospital stay. A symptom/sign-limited treadmill exercise test had been performed and CRP serum levels had been measured prior to discharge in all patients.

Results. During an average follow-up of 2.5 years (range 0.5-5 years), there were 8 major cardiac events (death or myocardial infarction) and 11 patients had recurrent unstable angina. Both exercise-induced myocardial ischemia [relative risk (RR) 3.02, 95% confidence interval (CI) 0.58-15.5, $p = 0.29$], and CRP levels ≥ 10 mg/l (RR 2.4, 95% CI 0.51-11.2, $p = 0.25$) showed a non significant association with major cardiac events. Low workload ischemia, however, was significantly associated with major cardiac events (RR 8.58, 95% CI 1.66-44.2, $p = 0.01$) and was also the only predictive variable for the combined endpoint of major events and recurrent angina (RR 2.57, 95% CI 1.02-4.44, $p = 0.045$). Among patients with low workload ischemia, the occurrence of major events was higher in those with high, compared to those with low, CRP levels, but the difference was not significant (28.6 vs 15.4%, $p = 0.64$).

Conclusions. In this study, pre-discharge myocardial ischemia at low workload was the single most important predictor of major cardiac events during long-term follow-up among patients with stabilized unstable angina. Increased serum CRP levels did not add further significant prognostic information in this specific group of patients with unstable angina, although this issue needs to be addressed in larger studies.

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Risk stratification of patients admitted to hospital because of unstable angina is one of the most debated and challenging topics in modern cardiology. Most previous studies relied on risk stratification at admission and several prognostic variables for the occurrence of short-term cardiac events have been described, including clinical and ECG findings¹⁻³, transient myocardial ischemia on Holter ECG monitoring^{4,5} and biochemical markers⁶⁻⁹. On the other hand, although variables obtained at admission can also be predictive of events at medium and long-term follow-up, optimal risk stratification of patients who do not experience events during hospital stay may require reassessment at discharge. Exercise test results¹⁰⁻¹⁴ and C-reactive protein (CRP) serum levels^{8,9,15-20} have both been reported to predict clinical events in these patients. No previous study,

however, carefully compared the prognostic value of exercise testing and CRP levels in this clinical setting.

Methods

Patients. We retrospectively reviewed data of 96 consecutive patients admitted to our coronary care unit because of unstable angina, who fulfilled the following inclusion criteria: 1) exercise test and measurements of CRP serum levels before discharge; 2) absence of in-hospital clinical events, including refractory angina; 3) no coronary revascularization procedures (either percutaneous or surgical) during hospital stay. Patients had had either prolonged angina, increasing anginal episodes at rest or recent worsening of effort angina. Acute myocardial infarction had been excluded

by repeated 12-lead standard ECG and enzymatic assessment (creatine kinase-MB).

Exclusion criteria included abnormalities on standard ECG, which could interfere with ST segment analysis (e.g., left bundle branch block, pacemaker, or relevant ST-T changes), a recent history (< 3 months) of myocardial infarction, evidence of inflammatory disease, and impossibility to exercise.

Exercise stress test. All subjects underwent a pre-discharge symptom/sign-limited exercise test, using a standard or modified Bruce protocol. The test was always performed with the patient being free from angina for at least 24 hours and while taking his/her usual drug therapy, which was at discretion of the attending physicians.

Leads II, V₂ and V₅ were monitored continuously throughout the test, and a 12-lead ECG was printed at the end of each stage, when clinically indicated, and at 1-min intervals in the recovery phase. Blood pressure was measured at baseline and during the last minute of each stage, unless otherwise indicated. The test was stopped in case of: 1) physical exhaustion; 2) progressive angina (Borg scale \geq 6); 3) ST segment depression > 2 mm; 4) clinically relevant events, including dyspnea, hypotension (a systolic blood pressure decrease > 20 mmHg compared to previous measurements), hypertension (systolic blood pressure > 240 mmHg and/or diastolic blood pressure > 140 mmHg), or ventricular arrhythmias (frequent or repetitive premature ventricular beats).

The following exercise variables were considered for prognostic assessment in this study: 1) exercise-induced myocardial ischemia, defined as horizontal or downsloping ST segment depression \geq 1 mm at 0.08 s from the J point in \geq 1 lead; 2) myocardial ischemia at low workload, defined as ST segment depression appearing prior to the end of the I stage of Bruce protocol (or III stage of modified Bruce protocol); 3) impaired effort tolerance, defined as interruption of exercise test before completing the II stage of Bruce protocol (or IV stage of modified Bruce protocol); 4) presence of both ST segment depression at low workload and impaired effort tolerance; 5) occurrence of angina.

C-reactive protein. CRP was measured on venous blood samples within more or less 2 days from the exercise test by an immunonephelometric method, using an N-high sensitivity CRP diagnostic assay (Dade Behring, Milan, Italy).

For prognostic assessment, in this study we considered both a cut-off level of CRP \geq 3 and a cut-off level of CRP \geq 10 mg/l, which were previously shown to be predictive of clinical events in unstable angina patients^{8,16}. However, since a cut-off level of CRP \geq 10 mg/l showed clearly better results, only data concerning this latter cut-off point are reported.

Endpoints and follow-up. Follow-up of patients was done over the telephone, with clinical information being obtained from patients themselves or their relatives. In case of events, or when necessary, clinical records were checked. The primary endpoint of the study was the occurrence of major cardiac events (i.e. cardiac death or non fatal myocardial infarction), whichever occurred first. Furthermore, the secondary endpoint of death, non fatal myocardial infarction or readmission to hospital because of recurrent unstable angina was also considered. The indication to revascularization procedures was at the total discretion of the attending physicians.

Statistical analysis. Differences of means between groups were evaluated by unpaired Student's t test, whereas Fisher's exact test was used to compare proportions. The association between clinical and exercise variables and endpoints was assessed by univariate Cox proportional hazard regression analysis and survival curves were obtained by Kaplan-Meier method and compared by log-rank test. No multivariate analysis was performed as myocardial ischemia at low workload was the only variable significantly correlated to cardiac events on univariate analysis. Patients who underwent coronary revascularization were censored at the time of percutaneous or surgical intervention. A p value of < 0.05 was always requested for statistical significance. Values are reported as mean \pm SD.

Results

General data. The main demographic and clinical data of the 96 patients included in the study are shown in table I. The group included 77 (80%) men and 19

Table I. Main clinical data of the study patients.

No. patients	96
Sex (M/F)	77/19
Age (years)	63.1 \pm 9.5
Drug therapy	
Nitrates	66 (69%)
Calcium-antagonists	67 (70%)
Beta-blockers	68 (71%)
ACE-inhibitors	48 (50%)
Exercise test	
ST segment depression	53 (55.2%)
Low workload ST depression	27 (28.1%)
Duration < II Bruce stage	31 (32.3%)
Angina	33 (34.4%)
CRP \geq 10 mg/l	30 (31.2%)
Coronary angiography	71 (74%)
0 vessel	5 (7%)
1 vessel	26 (37%)
2 vessels	21 (29%)
3 vessels	19 (27%)

CRP = C-reactive protein.

(20%) women, with a mean age of 63.1 ± 9.5 years. Exercise test was performed using standard Bruce protocol in 37 patients (38.5%) and modified Bruce protocol in 59 (61.5%).

Coronary angiography had been performed in 71 patients (74%) and showed 1-vessel disease in 26 (37%), 2-vessel disease in 21 (29%), and 3-vessel disease in 19 patients (27%). Epicardial coronary arteries were free from flow-limiting stenoses ($> 50\%$ of vessel diameter) in 5 patients (7%).

Exercise test and C-reactive protein results. Overall, 53 patients (55.2%) developed ST segment depression during exercise test, 27 of them at a low exercise level (28.1% of the total). An impaired effort tolerance was present in 31 patients (32.3%), and 15 patients (15.6%) showed both ST segment depression and low exercise tolerance. Angina during the test was induced in 33 patients (34.4%). High CRP levels (≥ 10 mg/l) were found in 30 patients (31.2%).

There were no differences in exercise results between patients with low (< 10 mg/l) or high (≥ 10 mg/l) CRP levels (Table II). Myocardial ischemia on exercise test was induced in 66.7% of patients with high and in 50% of patients with low CRP levels, respectively ($p = 0.18$), and angina was induced during the test in 40 and 32% of these two groups, respectively ($p = 0.49$). However, myocardial ischemia was induced at low workload more frequently in patients with high, compared to those with low, CRP values (46.7 vs 19.7% respectively, $p = 0.013$).

Primary endpoint. During an average period of 30.7 months (range 0.5-72 months) there were 8 major cardiac events among the 96 patients (8.3%), 4 of them were cardiac deaths and 4 non fatal myocardial infarction. No variable considered in this study, except low

workload ischemia, was significantly associated with cardiac events (Table III).

The primary endpoint occurred in 6 out of 53 patients (11.3%) with positive exercise test and in 2 out of 43 patients (4.6%) with negative exercise test (RR 3.02, 95% CI 0.58-15.5, $p = 0.29$). Low workload positivity, however, was associated with a significantly higher occurrence of cardiac events. Indeed, 6 out of 27 patients with ST segment depression at low workload (22.2%) had events versus 2 out of 69 patients (2.9%) with no ST or high workload ST segment depression (RR 8.58, 95% CI 1.66-44.2, $p = 0.01$).

CRP values ≥ 10 mg/l also tended to be associated with cardiac events, but the difference was not statistically significant. Indeed, coronary events occurred in 4 out of 30 patients (13.3%) with high and in 4 out of 66 patients (6.1%) with low CRP values (RR 2.4, 95% CI 0.51-11.2, $p = 0.25$).

In order to assess whether CRP measurements could add information to those derived by exercise testing, patients were divided into four groups, according to the presence or absence of low workload myocardial ischemia on exercise testing and to the presence of high or low levels of CRP. As shown in figure 1, the highest occurrence of events (28.6%) was observed among patients with both low workload ischemia and high CRP serum levels. However, there was no significant increase of events in this subgroup, compared to patients with low workload ischemia but low CRP serum levels (15.6%, $p = 0.64$).

Secondary endpoint. During the follow-up period, 11 patients were admitted to hospital because of recurrent unstable angina. Thus, 19 patients (19.8%) achieved the secondary endpoint of cardiac death, non fatal myocardial infarction or recurrent unstable angina. Furthermore, 27 patients (28.1%) underwent revascularization

Table II. Main exercise test results in patients with low or high C-reactive protein (CRP) levels.

	Low CRP (n=66)	High CRP (n=30)	p
Resting			
Systolic BP (mmHg)	135 \pm 22	141 \pm 29	0.44
Heart rate (b/min)	74 \pm 16	74 \pm 16	0.99
RPP (b/min*mmHg)	9993 \pm 2949	10 101 \pm 1670	0.92
1 mm ST segment depression			
Exercise time (s)	462 \pm 202	417 \pm 250	0.35
Systolic BP (mmHg)	171 \pm 37	168 \pm 31	0.76
Heart rate (b/min)	117 \pm 21	109 \pm 25	0.14
RPP (b/min*mmHg)	20 265 \pm 6561	18 788 \pm 6710	0.31
Peak exercise			
Exercise time (s)	488 \pm 194	479 \pm 248	0.86
Systolic BP (mmHg)	173 \pm 38	173 \pm 31	0.99
Heart rate (b/min)	120 \pm 21	114 \pm 25	0.24
RPP (b/min*mmHg)	20 999 \pm 6897	19 988 \pm 6715	0.50
ST segment depression (mm)	0.78 \pm 0.9	1.07 \pm 1.03	0.17

BP = blood pressure; RPP = rate-pressure product.

Table III. Relationship between variables and occurrence of major cardiac events (death or non fatal myocardial infarction).

	No. patients	RR	95% CI	p
Age ≥ 65 years				
Yes	5/43 (11.6%)	2.05	0.52-8.11	0.46
No	3/53 (5.7%)			
Sex				
Male	7/77 (9.1%)	1.73	0.23-13.21	0.99
Female	1/19 (5.3%)			
Exercise test				
Positive	6/53 (11.3%)	3.02	0.58-15.5	0.29
Negative	2/43 (4.6%)			
Low workload ischemia				
Yes	6/27 (22.2%)	8.58	1.66-44.2	0.005
No	2/69 (2.9%)			
Duration < II stage Bruce				
Yes	4/31 (12.9%)	2.10	0.56-7.84	0.27
No	4/65 (6.15%)			
Angina				
Yes	1/33 (3.0%)	0.27	0.04-2.12	0.26
No	7/63 (11.1%)			
CRP ≥ 10 mg/l				
Yes	4/30 (13.3%)	2.40	0.51-11.2	0.25
No	4/66 (6.1%)			

CI = confidence interval; CRP = C-reactive protein; RR = relative risk.

procedures during the follow-up. No variable considered in this study, except low workload ischemia, was significantly associated with this endpoint (Table IV).

The secondary endpoint occurred in 11 out of 53 patients (20.7%) with positive exercise test and in 8 out of 43 patients (18.6%) with negative exercise test (RR 1.36, 95% CI 0.54-3.41, p = 0.50), and it occurred in 7 out of 30 patients (23.3%) with high and in 12 out of 66 patients (18.2%) with low CRP values (RR 1.39, 95% CI 0.53-3.63, p = 0.50).

Yet, 9 out of 27 patients (33.3%) with ST segment depression at low workload had total cardiac events versus 10 out of 69 patients (14.5%) without low workload myocardial ischemia (RR 2.57, 95% CI 1.02-4.44, p = 0.045; Fig. 2).

Coronary angiography, ischemia, and clinical outcome. To address whether low workload myocardial ischemia could be helpful in risk stratification among patients with a known extension of coronary artery disease, we performed further analyses in 71 patients who had undergone coronary angiography. All 8 patients with major cardiac events and 14 patients with total cardiac events were included in this subgroup, in which all major cardiac events occurred among patients with multivessel disease [8 out of 40 patients (20%) vs 0 out of 31 patients without multivessel disease, p = 0.008]. Low workload ischemia was still associated with a significant increased risk of major events, which occurred in 6 out of 23 patients (26.1%) with, and in 2 out of 48 patients (4.2%) without low workload ischemia (RR 4.96, 95% CI 1.7-5.45, p = 0.012). Specifically, among

patients with multivessel disease, major events at follow-up occurred in 6 out of 13 (31.6%) with but in only 2 out of 19 patients (9.5%) without low workload ischemia (p = 0.12).

Total cardiac events occurred in 9 patients (22.5%) with and in 5 patients (16.1%) without multivessel disease (p = 0.71). Again, exercise low workload ischemia was associated with a significant increased risk of events, which occurred in 8 patients (34.8%) with and in 6 patients (12.5%) without low workload ischemia (RR 2.46, 95% CI 1.07-2.92, p = 0.04).

With regard to the whole population, both the mere presence of ischemia on exercise test and CRP ≥ 10 mg/l were not significantly associated with events even in this subgroup of patients (data not shown).

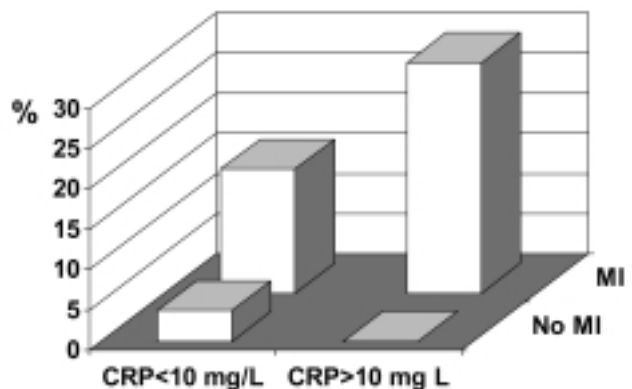
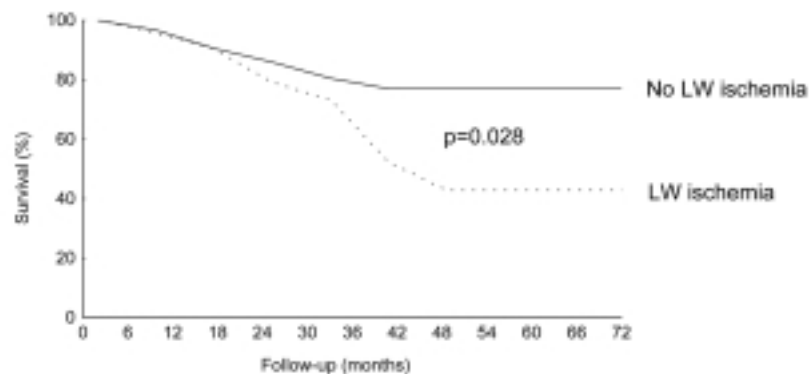


Figure 1. Frequency of major cardiac events, according to the presence or absence of myocardial ischemia (MI) at low exercise levels and to the detection of high or low serum levels of C-reactive protein (CRP).

Table IV. Relationship between variables and occurrence of the combined endpoint of death, non fatal myocardial infarction or recurrent unstable angina.

	No. patients	RR	95% CI	p
Age \geq 65 years				
Yes	10/43 (23.3%)	1.37	0.61-3.07	0.44
No	9/53 (5.7%)			
Sex				
Male	14/77 (18.2%)	0.69	0.28-1.68	0.42
Female	5/19 (26.3%)			
Exercise test				
Positive	11/53 (20.7%)	1.36	0.54-3.41	0.50
Negative	8/43 (18.6%)			
Low workload ischemia				
Yes	9/27 (33.3%)	2.57	1.02-4.44	0.045
No	10/69 (14.5%)			
Duration < II stage Bruce				
Yes	4/31 (12.9%)	0.78	0.29-2.07	0.77
No	4/65 (6.15%)			
Angina				
Yes	6/33 (18.2%)	0.88	0.37-2.10	0.77
No	13/63 (20.6%)			
CRP \geq 10 mg/l				
Yes	7/30 (23.3%)	1.39	0.53-3.63	0.50
No	12/66 (18.2%)			

Abbreviations as in table III.

**Figure 2.** Survival curves for the secondary endpoint of cardiac death, non fatal myocardial infarction or recurrence of unstable angina in patients with or without low workload (LW, prior to the end of the I stage of Bruce protocol) myocardial ischemia induced at pre-discharge treadmill exercise stress test.

Discussion

This is the first study that directly assessed the prognostic value of exercise test results and CRP levels in patients admitted to hospital because of unstable angina and discharged without any cardiac events, including coronary revascularization procedures. Of note is the fact that prognostic value of exercise test and CRP measurements was assessed in a long-term follow-up period (mean about 2.5 years) in these patients.

Major cardiac events (death or myocardial infarction) were found to occur more frequently both in patients with higher CRP levels (\geq 10 mg/l) and in those with exercise-induced myocardial ischemia. The differences, however, did not reach statistical significance, mostly because of the low number of patients included in the study. Yet, the occurrence of myocar-

dial ischemia at low workload during exercise test was found to be highly and significantly predictive of major cardiac events, and it was also the only variable predictive of the occurrence of the combined endpoint of death, non fatal myocardial infarction or recurrent unstable angina.

Although the lower number of patients precluded adequate analysis, the predictive value of low workload ischemia was confirmed when evaluating only those who underwent coronary angiography. Subgroup analysis revealed that major cardiac events occurred only in those with multivessel disease. However, there was a low occurrence of death/myocardial infarction in those without (9.5%), compared to those with low workload ischemia (31.6%) also in this subgroup of patients. Although this difference did not achieve statistical significance, likely due to the low number of sub-

jects included in this analysis, it further suggests the usefulness of exercise testing in this clinical context.

Finally, it is worth noting that the combination of low workload ischemia and high CRP levels was associated with the highest occurrence of major cardiac events in this study (Fig. 1). Although there was no significant difference compared to patients with low exercise level ischemia and low CRP levels, we suggest that further studies could be helpful to assess whether high CRP levels may add prognostic information in patients with low level exercise-induced myocardial ischemia.

Exercise test and prognosis. There have been relatively few studies aimed at assessing the prognostic value of exercise test in unstable angina. Wilcox et al.¹¹ first reported that exercise results were predictive of the combined endpoint of death, non fatal myocardial infarction and revascularization procedures at 1 year of follow-up in 107 unstable angina patients. Nyman et al.¹², on the other hand, showed that the occurrence of major cardiac events at 1 year among 740 patients with acute coronary syndromes (unstable angina and/or non-Q wave myocardial infarction) was significantly greater in those with a positive exercise test, compared to those with a negative test.

Two other studies have previously shown significant predictive value of exercise results for the occurrence of major cardiac events at a short/medium-term follow-up in patients with acute coronary syndromes^{13,14}. In particular, in a large report on 766 patients enrolled in the FRISC study, Lindhal et al.¹⁴ found that the combination of low exercise tolerance and exercise-induced myocardial ischemia was highly predictive of death and of the combined endpoint of death or non fatal myocardial infarction, independently of serum troponin T levels.

Our data confirm the importance of exercise results in risk stratification of patients with unstable angina. In particular, our data stress the importance of myocardial ischemia at low exercise levels, which was associated with a significant 8-fold increase in the risk of major coronary events and 2.6-fold increase in total cardiac events. Moreover, our findings highlight the very low occurrence of major cardiac events (< 2% per year) at follow-up in stabilized unstable angina patients with no signs of myocardial ischemia, and, even more in those with no ischemia at low exercise level (around 1%) at pre-discharge exercise testing.

C-reactive protein and prognosis. Several studies have recently shown that increased CRP values at admission in patients with acute coronary syndromes are predictive of the occurrence of major cardiac events during hospital stay^{8,17,19} and at short/medium-term follow-up¹⁶⁻¹⁸. Importantly, the prognostic value of CRP has been shown to be independent of troponin levels^{8,16-18}. Furthermore, some data have also reported that CRP

levels measured at discharge in patients with unstable angina are predictive of the occurrence of cardiac events at a medium/long-term follow-up^{15,20,21}.

A major limitation deriving from these studies is that very different cut-off levels of CRP (from 3 to 15.5 mg/l) have been considered or found to be prognostically relevant, making difficult the recommendation about the CRP level that should be considered for risk stratification in unstable angina. Again, differences in patient selection (only unstable angina vs acute coronary syndrome), and in the method used for CRP measurements may have influenced the different findings observed in the studies.

In our study, major coronary events tended to occur more frequently in patients with high (≥ 10 mg/l) than in those with low CRP values, but the differences did not reach statistical significance. On the other hand, there was no increase in the risk of total events (which included recurrence of instability) in our patients with high CRP serum levels. The reasons for the limited, non significant prognostic value of CRP in our study are not clear, but the small number of patients included may have precluded the possibility for differences to reach statistical significance.

Interestingly, in our study ischemia at low workload was induced more frequently in patients with high CRP levels. This could be due to the fact that the presence of a significant inflammatory state can delay the stabilization of unstable coronary plaques. Alternatively, as suggested by recent findings²², increased CRP serum levels may favor coronary vasoconstriction at the level of coronary plaques, thus facilitating exercise-induced myocardial ischemia.

Exercise test, C-reactive protein and prognosis. Although both CRP levels and exercise test results have been reported to be predictive of events in unstable angina, no previous study carefully assessed the relative role of these two variables in risk stratification of these patients.

Bazzino et al.²¹ recently reported that CRP levels at discharge was the only independent predictor of major cardiac events in 139 patients with unstable angina, whereas stress test results did not add significant information to CRP levels. However, there are significant differences between this study and ours, including a higher cut-off for CRP (> 15 mg/l) and a shorter follow-up (3 months). Furthermore, in that previous study, patients underwent either exercise test or echocardiographic dobutamine stress test, and, for statistical assessment, only "positivity" for myocardial ischemia during stress testing was considered, which was defined as the complex occurrence of an ST segment depression associated with angina, signs of "abnormal cardiac performance", exercise capacity < 4 METs, or abnormal blood pressure response²¹, making any comparison with our data impossible.

Limitations of the study. Some limitations of our study are to be taken into account. First, our study included a small number of patients and, therefore, our findings need to be confirmed in larger populations of patients. Second, this was a retrospective study; thus, although unlikely, selection biases, possibly influencing the results, cannot be completely excluded; furthermore, careful assessment of other clinical and laboratory variables (in particular, left ventricular function and troponin levels) could not be attempted. Finally, it should also be considered that our patients were studied under their usual drug therapy, but, at present, it is not clear how this can influence risk assessment in unstable angina.

In conclusion, our data show that low-level exercise myocardial ischemia was the only significant predictive variable of major cardiac events in stabilized patients admitted with unstable angina. Increased serum CRP levels do not seem to add further significant prognostic information in this specific group of patients with unstable angina.

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