Prognostic Factors in Unstable Angina with Dynamic Electrocardiographic Changes. Value of Fibrinogen

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Introduction and objectives. The prognosis of unstable angina varies between series depending on the inclusion criteria and management protocol used. The aim of this study was to analyze in-hospital events and their predictors in a homogeneous single-center series of patients with unstable angina.

Material and methods. A total of 246 patients with the following inclusion criteria were studied: *1)* resting anginal pain, *2)* transient electrocardiographic changes during anginal pain, *3)* normal CK-MB levels and *4)* exclusion of postinfarction angina. All patients were treated with aspirin and enoxaparin (1 mg/kg/12 h). Coronary angiography was performed in the case of recurrent angina or ischemia in Bruce I-II stage during the predischarge effort stress test. The variables recorded were risk factors, history of ischemic heart disease, history of coronary surgery, ECG upon admission, and fibrinogen.

Results. During the hospital stay the following events were recorded: 36% recurrent angina, 58% cardiac catheterization, and 5,7% major events (infarction or death). Multivariate analysis found recurrent angina to be more frequent in patients with a history of coronary bypass surgery (p = 0.004. OR = 22; CI 95%, 3-182), ST-segment changes (p = 0.01. OR = 4.7, CI 95%; 1.4-15.9) and higher fibrinogen (p = 0.002. OR = 1,4, CI 95%; 1.1-1.7). Fibrinogen was the only variable related to cardiac catheterization (p = 0,009. OR = 1.3. CI 95%, 1.1-1.6) and major events (p = 0.001. OR = 2.0. CI 95%, 1.4-3.1).

Conclusions. *1)* Unstable angina with electrocardiographic changes was associated to a high rate of in-hospital events. *2)* Fibrinogen was related to any event, and previous by-pass surgery and ST changes were related to recurrent angina.

Key words: *Unstable angina. Prognosis. Electrocardiography. Fibrinogen.*

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Factores pronósticos en la angina inestable con cambios dinámicos del electrocardiograma. Valor del fibrinógeno

Introducción y objetivos. El pronóstico de la angina inestable varía entre diferentes series según los criterios de inclusión. El objetivo ha sido evaluar los episodios hospitalarios y sus predictores en una serie homogénea de angina inestable.

Material y métodos. Se incluyó a 246 pacientes consecutivos con los siguientes criterios: *a)* dolor anginoso en reposo; *b)* cambios electrocardiográficos dinámicos durante el dolor; *c)* CK-MB normal, y *d)* angina postinfarto excluida. Se trataron con aspirina y enoxaparina (1 mg/kg/12 h) y se efectuó coronariografía en caso de angina recurrente o isquemia en el estadio I-II de Bruce en el test de esfuerzo prealta. Se recogieron los factores de riesgo, historia previa de cardiopatía isquémica, historia de cirugía coronaria, electrocardiograma durante el dolor y fibrinógeno.

Resultados. Durante el ingreso se presentaron los siguientes episodios: 36%, angina recurrente; 58%, cateterismo cardíaco y 5,7%, episodios mayores (infarto o muerte). Mediante análisis multivariado se observó que la angina recurrente fue más frecuente con antecedentes de cirugía coronaria (p = 0,004; OR = 22; IC del 95%, 3-182), desviación del segmento ST (p = 0,01; OR: 4,7; IC del 95%, 1,4-15,9) y mayor fibrinógeno (p = 0,002; OR = 1,4; IC del 95%, 1,1-1,7). El fibrinógeno fue la única variable relacionada con la necesidad de cateterismo (p = 0,009; OR = 1,3; IC del 95%, 1,1-1,6) y episodios mayores (p = 0,001; OR = 2,0; IC del 95%, 1,4-3,1).

Conclusiones. *a)* La angina inestable con cambios electrocardiográficos se acompaña de una alta tasa de episodios hospitalarios, y *b)* los valores elevados de fibrinógeno se asocian con todos los episodios desfavorables, y los antecedentes de cirugía coronaria y la desviación del ST con angina recurrente.

Palabras clave: *Angina inestable. Pronóstico. Electrocardiografía. Fibrinógeno.*

ABBREVIATIONS

CK: creatinkinase.
OR: odds ratio.
CI: confidence interval.
ECG: electrocardiogram.
RR: relative risk.
ROC: receiver operator characteristic.

INTRODUCTION

Unstable angina is one of the most frequent reasons for hospital admission, and its course can also be complicated by a high incidence of inpatient cardiac events. Treatment of unstable angina is controversial, raising issues such as whether treatment combining heparin and aspirin is useful,[1] the use of low molecular weight heparin,[2,3] the use of IIb-IIIa receptor antagonists,[4,5] the choice of a conservative strategy vs an interventionist strategy,[6-9] and the new humoral prognostic markers.[10]

The diversity of study design means studies regarding unstable angina must be performed with caution, particularly with regard to the following data: *a)* heterogeneity of inclusion criteria, given that some studies do not require the presence of electrocardiography changes during the occurrence of chest pain to classify the episode as unstable angina,[3,6,11-13] and others include patients with unstable angina and non-Q-wave infarct;[1-8,12,14,15] *b)* heterogeneity of medical treatment, which in many cases is left to the discretion of the treating physician,[16] and *c)* heterogeneity in the indication for cardiac catheterization, which in many cases is also left to the discretion of the treating physician.[3,5,12,14,15,17] Given the differences encountered on these points in various studies, the frequency rate of hospital episodes shows a certain variability from one series to the next.

Our study includes a homogenous series of patients with pure unstable angina, excluding patients non-Q-wave infarct and high risk patients, and with the requirement that dynamic changes had to be evident on electrocardiogram (ECG) during the pain episode for the patient to be included in the study; by using these criteria we attempted to reduce the possibility of including patients with non-coronary chest pain. Anti-thrombotic treatment consisted of the administration of aspirin and enozaparin, and a conservative strategy was followed with regard to cardiac catheterization. The study aim was to evaluate the frequency of inpatient cardiac events and the predictors of same.

MATERIAL AND METHODS

Study group

From January 17, 1999 to December 18, 2001, 246 consecutive patients were admitted to our hospital with the diagnosis of unstable angina, according to the following criteria: *a)* anginous chest pain at rest; *b)* dynamic electrocardiographic changes during the pain episode; *c)* normal CK-MB values (acute myocardial non-Q-wave infarct was excluded), and *d)* the absence of a history of acute myocardial infarct for 30 days previously (post-infarct angina excluded). For inclusion in the study, an ECG was required during the pain episode that showed signs suggestive of ischemia, such as depression or elevation of the ST segment=0.1 mV, or inversion of the T-wave=0.1 mV. The CK-MB was determined upon the patient´s arrival in the emergency room, and at 8, 12, 18 and 24 hours after initiation of the pain, and in all cases the value was less than the upper limit of normal according to the protocol of our hospital (CK-MB activity <6% of total CK).

Treatment protocol

Upon admission, all patients received treatment with aspirin, enoxaparin (1 mg/kg/12 hours), intravenous nitroglycerine, and beta-blockers or calcium antagonists. In no case were IIb-IIIa receptor antagonists administered. For patients with an ST segment elevation, this rapidly dropped (in less than 20 minutes) with the administration of nitroglycerine, and therefore no patient required fibrinolitic treatment.

Analysis

Forty-eight hours after admission (range 24 to 72 hours) routine analysis, including fibrinogen analysis, was performed. In order to determine the fibrinogen level, blood was collected with sodium citrate at a ratio of 1:10. The sample was processed by the coagulant formation technique in an automatic coagulometer, and measurements were made by the optical method. The variation coefficient for our laboratory is less than 10%.

Indications for cardiac catheterization

The initial attitude was conservative. Thus, coronary angiography and revascularization (if anatomically possible) were indicated without previous stress test only in the case of recurrent angina despite medical treatment. Before discharge, those patients stabilized with medical treatment underwent a symptom-limited stress test according to the Bruce protocol, and patients with Bruce stage I-II ischemia were selected to undergo coronary angiography.

Collection of clinical data

Coronary risk factors and a history of ischemic heart disease and cardiac surgery were noted in the clinical history. During hospital admission the following episodes were made note of: *a)* recurrent angina, defined by recurrent chest pain with transitory changes on ECG but without CK-MB elevation; *b)* the need for cardiac catheterization, and *c)* a major episode, defined by acute myocardial infarct (recurrent chest pain with CK-MB elevation) or death.

Statistical analysis

Quantitative variables were expressed as mean ±standard deviation (SD) and were compared by the ANOVA test. Qualitative variables were expressed as percentages and were compared by the χ^2 test. Relative risk (RR) was determined with confidence intervals (CI) of 95%. The best cut-off points for the quantitative fibrinogen value that predicted the risk of episodes was determined by using receiver operator characteristic (ROC) curves. Multivariate analyses were performed by binary logistical regression analysis, and we included those variables that on univariate analysis showed a value of $P<.1$; the odds ratio (OR) and 95% CI were calculated.

In all cases $P<.05$ was considered significant. For statistical analysis, the SPSS 9.0 (Chicago, Illinois) statistical package was used.

RESULTS

Population characteristics

Table 1 shows the population characteristics of patients included in the study. Mean age was 67±10 years.

The initial changes on ECG that justified inclusion in the study were an isolated T-wave inversion in 50 patients (20%) and deviation in the ST segment in 196 (80%), 146 with an ST segment decline (60%) and 50 with an ST segment increase (20%).

Episodes during hospital admission

Eighty-eight patients (36%) presented with recurrent angina, and 14 patients (5.8%) with major cardiac events, 8 with non-fatal acute myocardial infarct, and 6 patients died. Cardiac catheterization was performed on 142 patients (58%), coronary angioplasty was indicated in 60 patients (24%), and cardiac surgery was indicated in 32 patients (13%). One infarct and 1 death occurred following angioplasty, and 2 deaths occurred following surgery; the remaining 10 major episodes occurred before cardiac catheterization. One death occurred in the first 24 hours following admission, before a blood sample could be obtained to determine the fibrinogen level.

TABLE 1. **Population characteristics**

Clinical history	
Age	67±10
Men	156 (63%)
Smoker	62 (25%)
Hypertension	151 (61%)
Hypercholesterolemia	123 (51%)
Diabetes mellitus	92 (37%)
History of ischemic heart disease	109 (44%)
History of heart surgery	12 (5%)
ECG	
T-wave inversion	50 (20%)
ST deviation	196 (80%)
ST decline	146 (60%)
ST increase	50 (20%)

Predictors of episodes

Table 2 shows the predictors of current angina by means of univariate analysis. Recurrent angina occurred more frequently in patients with a history of ischemic heart disease (41% vs 31%; $P=.1$; RR=1.5; 95% CI, 0.9 to 2.6), a history of cardiac surgery (83% vs 33%; $P=.001$; RR=10.0; 95% CI, 2.1 to 46.7), ST segment deviation (41% vs 14%; $P=.0001$; RR=4.3; 95% CI, 1.9 to 10.1), and a higher fibrinogen level (5.2 g/L±1.8 g/L vs 4.4 g/L±1.4 g/L; $P=0.001$, RR=1.4, 95% CI, 1.1-1.7). By multivariate analysis (including the variables of history of ischemic heart

TABLE 2. **Predictors of recurrent angina by univariate analysis**

	Yes	No	P	RR	95% CI
Clinical history					
Age	67±10	66±10	ns		
Men	36%	36%	ns		
Hypertension	34%	39%	ns		
Smoker	34%	36%	ns		
Diabetes mellitus	34%	37%	ns		
Hypercholesterolemia	33%	32%	ns		
History of ischemic heart disease	41%	31%	0.1	1.5	0.9-2.6
History of surgery	83%	33%	0.001[a]	10.0	2.1-46.7
ECG					
ST deviation[b]	41%	14%	0.0001[a]	4.3	1.9-10.1
ST decline	42%	27%	0.02	1.9	1.1-3.4
Fibrinogen, g/L	5.2±1.8	4.4±1.4	0.001[a]	1.4	1.1-1.7

RR indicates relative risk; CI, confidence intervals.
[a]Variables independently related on multivariate analysis.
[b]Includes both ST increase and decline.

disease, history of heart surgery, deviation of ST segment, and fibrinogen level), history of heart surgery (*P*=0.004, OR=22; 95% CI, 3 to 182), ST segment change (*P*=.01; OR=4.7; 95% CI, 1.4 to 15.9), and fibrinogen level (*P*=.009; OR=2.4; 95% CI, 1.3 to 4.6) were independent predictors. The area below the ROC curve for the fibrinogen level that predicted recurrent angina was 0.63±0.04 (*P*=0.004), and the best cut-off point for a fibrinogen level predictor was ≥4.5 g/L (43% vs 26%; *P*=.02; RR=2.1; 95% CI, 1.2 to 3.9).

Table 3 presents the variables related to the need for cardiac catheterization on univariate analysis. A history of heart surgery (92% vs 56%; *P*=.02; RR=8.6; 95% CI, 1.1 to 68.3) and a higher fibrinogen level (4.9 g/L±1.5 g/L vs 4.3 g/L±1.5 g/L; *P*=.009; RR=1.3; 95% CI, 1.1 to 1.6) significantly increased the probability of the need for cardiac catheterization. On multivariate analysis (including the variables of a history of heart surgery and increased fibrinogen), a higher fibrinogen level (*P*=.01; OR=2.1; 95% CI 95%, 1.2 to 3.9) was the only independent predictor variable. The fibrinogen level in the area below the ROC curve that predicted the need for cardiac catheterization was 0.61±0.04 (*P*=.007), and the best cut-off point for a predictor fibrinogen value was ≥4.5 g/L (66% vs 50%; *P*=.03; RR=2.0; 95% CI, 1.1 to 3.6).

Major events (Table 4) were only related to a higher fibrinogen value (6.7 g/L±1.8 g/L vs 4.6±1.5 g/l; *P*=.001; RR=2.0; 95% CI, 1.4-3.1), although there was a non-significant tendency toward more major events in those patients with an ST segment deviation (6.6% vs 2.0%; *P*=.2). The area below the ROC curve for fibrinogen as a predictor of a major episode was 0.83±0.07 (*P*=.001), and the best cut-off point was a fibrinogen value ≥5 g/L (10.8% vs 1.6%; *P*=.007; RR=7.7; 95% CI, 5-38.7).

TABLE 3. **Predictors of the need for cardiac catheterization during hospital admission by univariate analysis**

	Yes	No	P	RR	95% CI
Clinical history					
Age	66±10	68±11 ns			
Men	60%	54%	ns		
Hypertension	56%	60%	ns		
Smoker	57%	58%	ns		
Hypercholesterolemia	59%	51%	ns		
Diabetes mellitus	61%	56%	ns		
History of ischemic heart disease	61%	55%	ns		
History of cardiac surgery	92%	56%	0.02	8.6	1.1-68.3
ECG					
ST deviation	60%	50%	ns		
Fibrinogen, g/L	4.9±1.6	4.3±1.5	0.009[a]	1.3	1.1-1.6

RR indicates relative risk; CI, confidence intervals.
[a]Variables with an independent relationship on multivariate analysis.

Predictive value of fibrinogen

The study group was divided into fibrinogen quartiles (<3.5, 3.5-4.3, 4.4-5.5, >5.6 g/L) (Figure 1). When the fibrinogen level increased, we noted a progressive increase in the rate of recurrent angina (23%, 27%, 30%, and 50%; *P*=.02; RR of the fourth vs the first quartile =3.3; 95% CI, 1.3 to 8.1; *P*=.01), the need for catheterization (35%, 58%, 61%, and 66%; *P*=.02; RR of the fourth quartile vs the first quartile =3.6; 95% CI, 1.5 to 8.5; *P*=.004), and major episodes (0%, 2%,1%, 4.5%, and 12%; *P*=.04; RR of the fourth quartile vs the first quartile =2.0; 95% CI, 1.6 to 2.4; *P*=0.03).

DISCUSSION

The principal findings of our study were as follows: *a)* the hospital course of patients with unstable angina with dynamic electrocardiographic changes who are initially treated conservatively is complicated by a high rate of cardiac episodes such as recurrent angina in 36% of cases, the need for catheterization in 58%, and major episodes in 5.4%, and *b)* elevation of fibrinogen levels is associated with all unfavorable episodes, while a history of cardiac surgery and a decline in the ST segment during the pain episode is associated with recurrent angina.

Natural history of unstable angina

The history of unstable angina varies from one study to another as a function of the inclusion criteria used. Our series analyzed patients with high-risk unstable angina by requiring the presence of dynamic

TABLE 4. **Predictors of major episodes during hospital admission via univariate analysis**

	Yes	No.	P
Clinical history			
Age	67±11	67±10	ns
Men	5.8%	5.6%	ns
Hypertension	5.3%	6.3%	ns
Smoker	4.8%	6.1%	ns
Hypercholesterolemia	5.0%	5.3%	ns
Diabetes mellitus	4.3%	6.5%	ns
History of ischemic heart disease	7.3%	4.4%	ns
History of cardiac surgery	8.3%	5.6%	ns
ECG			
ST deviation[a]	6.6%	2.0%	0.2
ST decline	6.2%	5.0%	ns
Fibrinogen, g/L	6.7±1.8	4.6±1.5	.0001

[a]Includes both ST increase and decline.

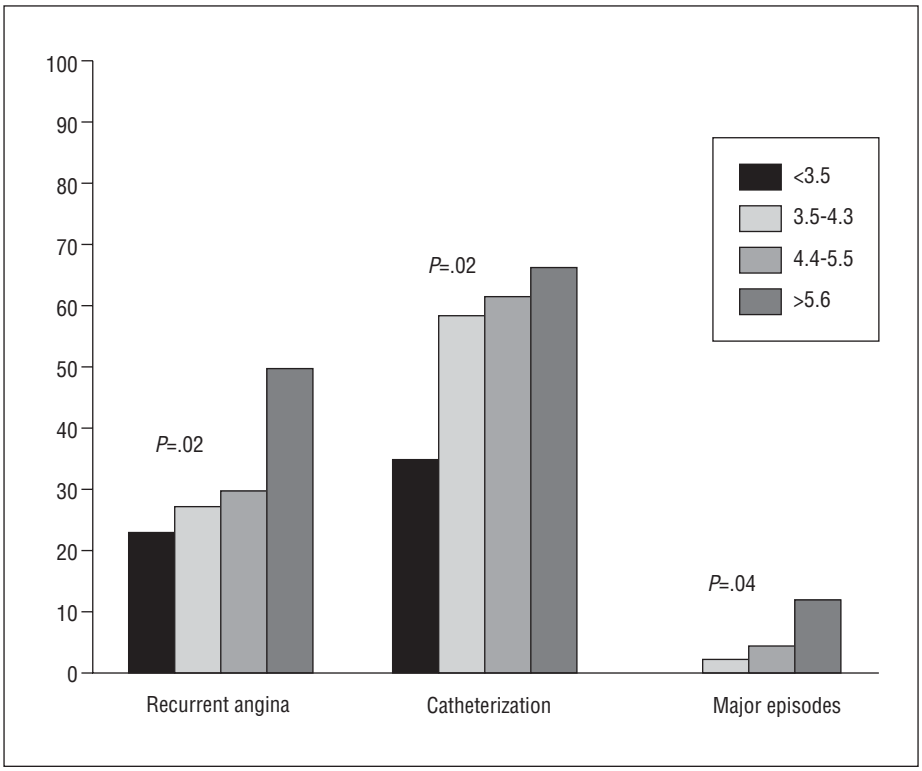

Fig. 1. Division of the study population into quartiles by fibrinogen values (<3.5, 3.5-4.3, 4.4-5.5, >5.6 g/L). When the fibrinogen level increased, a progressive increase in the rate of recurrent angina was observed (23%, 27%, 30%, and 50%; *P*=.02; RR of the fourth quartile vs the first quartile =3.3; 95% CI, 1.3 to 8.1; *P*=.01), the need for catheterization (35%, 58%, 61%, and 66%; *P*=.02; RR of the fourth quartile vs the first quartile =3.6; 95% CI, 1.5 to 8.5; *P*=.004), and major episodes (0%, 2.1%, 4.5%, and 12%; *P*=.04; RR of the fourth quartile vs the first quartile =2.0; 95% CI, 1.6 to 2.4; *P*=.03).

electrocardiographic changes during the pain episode for patient inclusion in the study. In other studies, documentation of electrocardiographic changes during the episode of chest pain was not a requirement for inclusion of patients;[11-14] eliminating this requirement may result in the inclusion of lower-risk patients or of patients with non-coronary chest pain. On the other hand, we excluded patients with non-Q-wave infarct. Other series group together unstable angina and non-Q-wave infarct.[1-8,15] Although theoretically both entities share the same pathogenesis, which consists of serious coronary stenosis without occlusion and with no or a small amount of myocardial necrosis,[18-20] could produce extensive infarcts, in spite of Q-waves not being observed on surface ECG, a prognostic implication that is clearly different from that of pure unstable angina without necrosis or with minimal necrosis.

Our study finding of a rate of 36% for recurrent angina during admission is greater than that reported in other series.[1,3,21] Osler et a[11] found a rate of 17% for recurrent angina on meta-analysis that included studies of unstable angina or non-Q-wave infarct treated with aspirin and intravenous heparin. In the ESSENCE study,[3] the rate of inpatient recurrent angina was 13% in the subgroup treated with aspirin and enoxaparin (the same treatment regimen as in our study). The differences are explained by the inclusion criteria used. Therefore, our patient population would be very much exposed to recurrent ischemia, as the dynamic electrocardiographic changes without enzyme elevation would indicate serious ischemia and a myocardium at risk without necrosis.

In spite of the high incidence of recurrent angina, the frequency of major inpatient episodes is similar to[3,15] or lower than[1,4,5] that of other series that also included subgroups of patients treated with aspirin and subcutaneous or intravenous heparin. Probably the exclusion of patients with non-Q-wave infarct and post-infarct angina, on one hand, and the availability of a hemodynamic laboratory for urgent catheterization in the case of recurrent angina on the other, would justify this relatively lower incidence of major episodes in comparison with the high rate of recurrent angina.

History of heart surgery

In spite of the fact that our study only included 12 patients with a history of heart surgery, this variable was a potent predictor of recurrent angina and the need for cardiac catheterization. Eighty-three percent of patients with a history of heart surgery presented with refractory angina and 92% required catheterization. These data suggest the usefulness of a strategy of routine catheterization in cases of unstable angina with a previous history of an aortocoronary graft, although the possibility of successful revascularization are limited in these patients.[22] A history of heart surgery was not related to the occurrence of major episodes, probably due to the limited number of patients included in our study.

Dynamic ECG changes

The dynamic ECG changes recorded in our study were a decrease in ST segment in 60% of patients, an increase in ST segment in 20% of patients, and isolated T-wave inversion in the remaining 10% of patients. Data published in other studies shows a greater proportion of T-wave changes. Thus, in the TRIM study,[23] in the subgroup that presented with electrocardiographic changes, in 29% of patients there was an increase in the ST segment, 18% had a decrease in ST segment, and 53% had T-wave inversion. In the ESSENCE study,[3] of the subgroup of patients with electrocardiographic changes who were treated with enoxaparin, 10% showed an increase in the ST segment, 33% showed a decrease in the ST segment, and 57% showed T-wave changes, although in this study the subcategories of patients as a function of ECG were not mutually exclusive.

In our series, changes in the ST segment increased the probability of recurrent angina in comparison with T-wave changes. In series that included 60%[23] and 28%[24] of patients without electrocardiographic changes, the deviation of the ST segment was associated with recurrent ischemia, while T-wave inversion had no predictive value. The ST segment changes have also been related to the occurrence of major episodes,[25-27] although we only found a tendency that did not reach statistical significance. Two factors could explain the lack of statistical significance: *a)* the exclusion of patients with non-Q-wave infarcts and post-infarct angina, and *b)* the low rate of major episodes that limited the statistical power of the analysis of its predictors.

Fibrinogen

AN increased fibrinogen level is a predictor of a poor prognosis for patients with unstable angina and non-Q-wave myocardial infarct.[28-31] The relationship of various risk factors to fibrinogen has been described, such as age, smoking, obesity, a sedentary lifestyle, diabetes, and arterial hypertension.[32] Nevertheless, after adjustment for the principal risk factors, fibrinogen remained an independent risk factor for acute myocardial infarction and death in patients with ischemic heart disease.[33] In our study, elevation of fibrinogen levels increased the probability of all unfavorable inpatient episodes, independently of coronary risk factors, and was the only variable associated with major cardiac events. Three mechanisms may explain the relationship between fibrinogen and a poor prognosis:[29] *a)* a marker for a state of hypercoagulability that favors coronary thrombosis; *b)* acute phase reactant due to a high inflammatory reaction in the atheromatous plaque of a coronary vessel, and *c)* an acute phase reactant due to myocardial damage. Given that we excluded patients with non-Q-wave infarcts, this last mechanism does not appear to be the culprit in our study.

Clinical implications

Currently, there is controversy regarding whether to follow a conservative or interventionist strategy in the treatment of patients with unstable angina and non-Q-wave infarcts.[6-9] In our series, cardiac catheterization was performed in 58% of patients, in spite of an initially conservative treatment strategy. This data suggests that in high-risk unstable angina, defined by dynamic electrocardiographic changes, routine catheterization upon admission may be appropriate, at least for the subgroup of patients with markers for a poor prognosis during their hospital course: a history of heart surgery, ST segment changes on the initial ECG, and an increase in fibrinogen value.

Limitations

When we began our study, determination by means of troponin testing was not available in our hospital. Therefore, patients with non-Q-wave infarcts were excluded via CK-MB values. If there a troponin test had been available, some patients might possibly have been placed in the category of «micro infarct,» or infarct per the new definition of acute myocardial infarct.[34] Similarly, obtaining samples for the determination of fibrinogen values was not homogenous with respect to the time of hospital admission, and there was a range of 24 to 72 hours from the time of admission to the extraction of blood for the sample.

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