ISCHEMIC HEART DISEASE

Prognostic Value of Fibrinogen in Patients Admitted with Suspected Unstable Angina and Non-Q-Wave Myocardial Infarction

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Introduction and objective. In recent years, the relation between biological markers of inflammation and prognosis in patients suffering from acute coronary syndromes has been investigated. The aim of this study was to evaluate the association between baseline fibrinogen concentrations and the development of clinical events in patients admitted with suspicion of unstable angina and non-Q-wave myocardial infarction.

Material and method. Levels of fibrinogen at enrollment were analyzed in 325 consecutive patients with acute coronary syndromes. Fibrinogen values were divided into tertiles and the incidence of clinical events was evaluated at each level. The combination of death and/or myocardial infarction was the main endpoint.

Results. Fibrinogen levels were significantly higher in patients who subsequently had myocardial infarction, cardiac death, or both during follow up. The probabilities of death and/or myocardial infarction were 6%, 13%, and 29% (p < 0.0001), respectively, in patients grouped by fibrinogen tertiles (304, 305-374 and 375 mg/dl). Multivariate predictors of combined events were age, previous angina, ST-segment depression in the admission ECG, and fibrinogen into tertiles. The adjusted *hazard ratio* (95% CI) for patients in the upper tertile was 4.8 (1.6-14; p = 0.004).

Conclusions. High fibrinogen levels were related to a less favorable long-term or short-term outcome in patients admitted for suspicion of unstable angina and non-Q-wave myocardial infarction. This association persists after adjustment for other classical risk factors such as age, prior angina, and ST-segment depression in the ECG.

Key words: *Fibrinogen. Unstable angina. Myocardial infarction. Coronary artery disease.*

Valor pronóstico del fibrinógeno en pacientes ingresados con sospecha de angina inestable o infarto de miocardio sin onda Q

Introducción y objetivo. Durante los últimos años se ha investigado la relación entre los marcadores biológicos de inflamación y el pronóstico en pacientes con síndromes coronarios agudos. Nuestro objetivo ha sido analizar la asociación entre las concentraciones plasmáticas de fibrinógeno y la aparición de episodios clínicos en pacientes ingresados con sospecha de angina inestable o IAM no Q.

Material y método. Analizamos el fibrinógeno al ingreso en 325 pacientes consecutivos ingresados con sospecha de síndrome coronario agudo. Los valores de fibrinógeno se dividieron en terciles y se evaluó la incidencia de episodios en cada estrato. Se realizó un seguimiento medio de 15 meses considerando como episodio principal el combinado de muerte y/o IAM.

Resultados. Los valores de fibrinógeno fueron significativamente mayores en los pacientes que presentaron IAM, muerte de causa cardíaca o el episodio combinado durante el seguimiento. El porcentaje de episodio combinado fue del 6, el 13 y el 29% (p < 0,0001) en pacientes estratificados por terciles de fibrinógeno (304, 305-374 y 375 mg/dl). Los predictores multivariados de episodio combinado fueron la edad, la angina previa, el descenso del segmento ST y el fibrinógeno en terciles. Un valor de fibrinógeno en el tercil superior se asoció al episodio con una *hazard ratio* de 4,8 (IC del 95%, 1,6-14; p = 0,004).

Conclusiones. Los valores elevados de fibrinógeno se asocian con un peor pronóstico a corto y largo plazo en pacientes ingresados con sospecha de angina inestable o IAM no Q. La asociación se mantiene tras ajustar por factores de riesgo clásicos como la edad, la angina previa y el descenso del segmento ST al ingreso.

Palabras clave: *Fibrinógeno. Angina inestable. Infarto de miocardio. Enfermedad coronaria.*

ABBREVIATIONS

ACS: acute coronary syndrome.
AMI: acute myocardial infarction.
RPC: reactive protein C.
CPK: creatinphosphokinase.
CCI: congestive cardiac insufficiency.
ECG: electrocardiogram.
CBRBHB: complete block of the right branch
    of the His bundle.
CAP: coronary angioplasty.
HR: *hazard ratio.*
RR: *relative risk.*

INTRODUCTION

Patients with acute coronary syndrome (ACS, unstable angina, and acute myocardial infarct [AMI] without persistent ST segment elevation), one of the most frequent reasons for admission to cardiac units,[1,2] represents a very heterogeneous and high-incidence group.

Various clinical, electrocardiographic, and laboratory variables have proven to be predictors of the risk of cardiovascular events in patients admitted for ACS.[3] Early treatment within the first hours of admission with anticoagulants and anti-plaque aggregates (both conventional and, more recently, supplemented by IIb-IIIa receptor antagonists) has achieved a decrease in the number of adverse events, with maximum efficiency apparent in selective groups of high-risk patients.[4] Risk should be ranked, therefore, according to data available at admission to accurately determine prognosis and to guide appropriate treatment.

Over the last few years, there has been particular attention to the relationship between the inflammation component of vulnerable plaque and atherosclerosis,[5-9] and several studies have shown that the classic markers of inflammation, such as fibrinogen or reactive protein C (RPC), typical reactive molecules in the acute phase, may be risk predictors for coronary events.[10-13]

Our aim was to analyze the association between plasma fibrinogen concentrations and the occurrence of clinical events (AMI or cardiac death) medium-term among patients admitted with suspected ACS.

MATERIALS AND METHODS

We performed a prospective observational study of 415 consecutive patients with suspected unstable angina (Braunwald class IIIb) or non-Q AMI admitted to the cardiac unit between November, 1997, and July, 1998. Patients with secondary angina or post-infarct angina were excluded in order to select a more homo-genous group of patients. The angina was of recent onset for all patients (<2 months) or progressive, with pain at rest within the last 24 hours, and the diagnosis was fundamentally clinical. To assure the spectrum of clinical presentation of primary unstable angina in the study group, electrocardiographic changes and documented previous coronary disease were not necessary for inclusion in the study. The diagnosis of non-Q AMI on admission was made if there was evidence of creatinphosphokinase (CPK) and CPK-MB (catalytic activity) values more than double the normal values together with a compatible clinical picture or ischemic ST segment changes, or both, with the development of new pathological Q-waves on serial testing up to a maximum of 12 hours after admission. Fibrinogen was determined at the time of admission to the emergency department before any treatment was initiated, and measurements were performed with turbidimetry.

Patients who did not have baseline fibrinogen available were excluded, as were those who presented with concurrent inflammatory disease or fever (>39 °C), had known neoplasia, chronic renal insufficiency (creatinine >2 mg/dL), or hepatic insufficiency (prothrombin time <50%), and those patients who were undergoing anticoagulant treatment, as all these conditions alter normal fibrinogen values. A total of 325 patients were included in the study.

A median follow-up period of 15 months (1-758 days) was established by telephone and review of clinical history. A combined cardiac death or AMI were considered principal events, and each was also analyzed separately. Follow-up was achieved in 100% of cases.

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) for those values that followed a normal distribution and as average, and as he 25th and 75th percentiles for those that were non-Gaussian. Qualitative variables were expressed as percentages. Comparison between qualitative variables was performed by χ^2 and between continuous variables by the Student t test (Mann-Whitney U test for those not following normal trends). To evaluate the individual contribution of various risk factors already known to affect the progression of the events under study, we performed a bivariate Cox regression analysis followed by a multivariate analysis, including those variables with a P value of less than 0.10 upon bivariate analysis together with values later considered to be relevant from a clinical point of view. The variables studied were: age, sex, presence of diabetes mellitus, dyslipemia, arterial hypertension, smoking, and peripheral arteriopathy; the existence of previous angina, previous AMI, previous congestive cardiac insufficiency (CCI), or revascularization (bypass or CAP/stent vs its

TABLE 1. **Baseline characteristics of the patient population**

Clinical variables	[N=325] n (%)
Age	65±11
Sex (?)	235 (72)
Diabetes	98 (30)
Dyslipemia	172 (53)
AHT	158 (49)
Smoking	85 (26)
Peripheral a.	59 (18)
Previous angina	199 (61)
Previous AMI	119 (37)
Previous CCI	80 (25)
Revascularization	56 (17)
CAP	32 (10)
Surgery	28 (9)
Clinical presentation	
Unstable angina	283 (87)
Non-Q AMI	42 (13)
ECG on admission	
Normal	89 (27)
T-wave alteration	82 (25)
Decrease in ST	102 (31)
Increase in ST	25 (8)
CBRBHB	12 (4)
Other (pacemaker, etc.)	15 (5)

AHT indicates arterial hypertension; Peripheral a., peripheral arteriopathy; AMI, acute myocardial infarction; CCI, congestive cardiac insufficiency; CAP, coronary angioplasty; CBRBHB, complete block of the right branch of the His bundle; Revascularization, CAP or previous heart surgery.

absence, or both); the form of clinical presentation (initial effort or progressive angina, angina at rest, or non-Q AMI); the ECG upon admission (normal, T-wave inversion, drop in ST segment, increase in ST segment, complete block of the right branch of the His bundle [CBRBHB]); and various biochemical parameters (CPK, cholesterol, triglycerides, and creatinine, in addition to fibrinogen). The fibrinogen tertiles were calculated and the association of each with the episodes under study was analyzed, comparing survival rate without combined cardiac events by Kaplan-Meier analysis (log-rank test). In the same manner, an ROC curve was created to determine at what cut-off point the fibrinogen would have the greatest sensitivity and specificity for predicting the event.

RESULTS

Baseline characteristic of the patient population in our study are listed in Table 1.

Coronary angiography was performed according to the criteria of the treating cardiologist in 157 (48%) of the patients. Of these, 40 patients (25%) had single vessel disease, 30 (19%) had 2-vessel disease, 45 had (29%) 3-vessel disease, and 11 patients (7%) had dise-

ase of the common left trunk. In the remaining 31 patients (20%), the coronary tree did not show significant lesions. This last subgroup continued to be considered as patients with ACS due to particular patient characteristics (previous AMI, previous CAP, evolving changes on ECG, or positive electric stress test, or both, or more than 1 criterion).

During hospital admission coronary intervention was performed (CAP or stent, or both) in 47 patients and coronary revascularization surgery in 24 patients. Percutaneous intervention was performed in 7 additional patients and scheduled surgery was performed on 15 patients, so that at the end of follow-up the percentage of patients with CAP or stent, or both, was 17% and for aortocoronary bypass, 12%. Eighty-eight patients (27%) were re-admitted for angina in the course of the study.

During a medium-term followup of 15 months, 23 infarcts (7%) were recorded. Seven of these patients died during the course of the study, 5 within the first 72 hours following AMI and the other 2 at 3 and 5 months after surviving a non-fatal AMI. There were 36 deaths due to cardiac causes (11%) and 52 patients (16%) had a combined episode (cardiac death and cardiac AMI, or both). Of the 36 deaths, 9 (3%) occurred during hospitalization–all within the first 72 hours–and the remaining 27 (8%) occurred after hospital discharge.

Fibrinogen values were significantly greater in those patients who presented with AMI, cardiac death, or a combined event during followup, the differences being more noticeable with regard to cardiac death (average: 415 vs 338 mg/dL; $P<.0001$). These discrepancies were already significant, except for AMI, in the first 48 hours of development (Table 2). The distribution of fibrinogen values showed a positive asymmetry as shown in the average and 25th and 75th percentiles.

Upon separating the patients according to diagnosis on admission (unstable angina or non-Q AMI), the differences remained significant for cardiac death and a combined event for both groups. The distance averages for these events was ≃65 mg/dL for unstable angina and a more obvious ≃90 mg/dL for non-Q AMI (Table 3).

Given the distribution, skewed to the right, of the fibrinogen values, we considered it appropriate to divide the sample into tertiles and evaluate the events at each of these defined levels. The cut-off points were less than 305 mg/dL (lower tertile), from 305 to 374 mg/dL (middle tertile), and y≥375 mg/dl (upper tertile). As seen in Figure 1, there is a growing progression in the occurrence of episodes from the lower to the upper tertile and, as was shown in the previous tables, said differences were more marked for cardiac death and combined events. In the same manner, survival free of cardiac death or AMI, or both (Kaplan-Meier, Log-Rank by level), with a much worse prognosis was evident in patients with fibrinogen in the upper tertile.

TABLE 2. Plasma fibrinogen values upon admission according to clinical events and the time of development of event

	Development in 1st 48 h			Development in followup (15 months)		
	N	Average (percentile 25-75)	P	N	Average (percentile 2-75)	P
AMI						
Yes	7	356 (333-419)	.3	23	377 (333-417)	.03
No	318	342 (286-394)		302	340 (284-394)	
Cardiac d.						
Yes	9	398 (382-514)	.002	36	415 (334-481)	<.0001
No	316	340 (285-393)		289	338 (283-382)	
Combined						
Yes	16	391 (356-443)	.003	52	393 (339-447)	<.0001
No	309	340 (284-393)		273	332 (280-381)	

Cardiac d. indicates cardiac death; Combined, cardiac death or infarct. P (Mann-Whitney U test).

The cut-off point determined by ROC curve was precisely at 375 mg/dL, which coincided with the beginning of the upper tertile (area, 0.73; $P<.0001$). Said cut-off point had a 70% sensitivity and specificity for predicting cardiac death.

To study the effects of other variables analyzed we performed a bivariate Cox regression analysis for each of the events studied (Table 4). Higher age, the presence of diabetes mellitus, decrease in the ST segment on ECG upon admission, and fibrinogen values in the middle tertile were bivariate predictors of AMU during followup. The variables associated with cardiac death and combined events were age, the presence of diabetes mellitus, peripheral arteriopathy, previous angina, AMI of CCI, decrease in ST on ECG on admission, and fibrinogen values greater than 375 mg/dL. The introduction of said variables in a Cox multivariant regression analysis (recalibrating the ECG for the presence vs the absence of decrease in the ST segment), and using this as a variable to predict a combined event resulted in the model shown in Table 5. The fibrinogen value maintained its significance in predicting cardiac death and AMI, or both. Values in the upper tertile ($\geq$375 mg/dL) represented a hazard ratio

(HR) of 4.8 (95% CI, 1.6 to 13.9) (P=.004) with respect to fibrinogen values less than 305 mg/dL. Values between 305 and 374 mg/dL did not imply a significantly greater risk in this study.

DISCUSSION

In our patients, fibrinogen values on admission were significantly higher in those who presented with AMI, cardiac death, or a combined event during medium-term followup of 15 months, differences that were already evident in the first 48 hours for cardiac death and combined events, and that were present both in the unstable angina subgroup and the non-Q AMI group. We identified a progressive increase in the frequency of events in accordance with progression from the lower tertile to the higher tertile of fibrinogen distribution, with the sharpest differences being in the highest tertile, with a 29% rate of death or AMI.

In recent years, the link between inflammation and the physiopathology of atherosclerosis and acute coronary syndromes has become more and more evident.[6,14-16] Lesions of the vascular wall cause, in part, the adhe-

TABLE 3. Plasma fibrinogen values upon admission according to events and clinical presentation (follow-up at 15 months)

	Unstable angina (n=283)			Non-Q AMI (n=42)		
	N	Average (percentile 25-75)	P	N	Average (percentile 25-75)	P
IAM						
Yes	19	363 (327-398)	.1	4	412 (378-535)	.1
No	264	333 (280-390)		38	358 (314-425)	
Cardiac d.						
Yes	30	398 (312-476)	.001	6	444 (430-571)	.003
No	253	332 (280-381)		36	355 (311-401)	
Combined						
Yes	44	391 (334-447)	<.0001	8	443 (385-536)	.006
No	239	328 (278-380)		34	351 (305-403)	

Cardiad d. indicates cardiac death; Combined, cardiac death or infarct. P (Mann-Whitney U test).

TABLE 4. **Association between variables and the development of events during followup**

	AMI					
	Yes (n=23)	No (n=302)	P	HR (95% CI)	Yes (n=36)	No (n=289)
Age	69±9	65±11	.04	1.05 (1.00-1.09)	73±7	64±11
Sex, male	10 (43)	80 (26)	.09	2.1 (0.9-4.6)	11 (31)	79 (27)
Diabetes	14 (61)	84 (28)	.002	3.8 (1.6-8.9)	21 (58)	77 (27)
Dyslipemia	11 (48)	162 (54)	.6	0.8 (0.4-1.9)	16 (46)	157 (55)
AHT	12 (52)	146 (48)	.7	1.2 (0.5-2.7)	24 (67)	134 (46)
Smoking	5 (22)	80 (26)	.7	0.8 (0.3-2.2)	3 (9)	82 (29)
Peripheral a.	5 (22)	54 (18)	.6	1.4 (0.5-3.7)	17 (55)	42 (17)
Previous angina	18 (78)	181 (60)	.09	2.3 (0.8-6.2)	32 (89)	167 (58)
Previous AMI	9 (39)	110 (36)	.7	1.2 (0.5-2.7)	21 (58)	98 (34)
Previous CCI	8 (35)	72 (24)	.1	1.9 (0.8-4.5)	23 (64)	57 (20)
Revascularization						
ACTP	2 (9)	30 (10)	.8	0.9 (0.2-3.7)	3 (8)	29 (10)
Surgery	0	28 (9)	.3	–	3 (8)	25 (9)
ECG on admission			.03			
Normal	6 (26)	83 (27)	–	–	6 (17)	83 (30)
T-wave change	1 (4)	81 (27)	.1	0.2 (0.02-1.5)	6 (17)	76 (28)
ST decrease	15 (65)	87 (29)	.05	2.5 (1.0-6.4)	19 (54)	83 (30)
ST increase	1 (4)	24 (8)	.6	0.5 (0.06-4.4)	1 (3)	24 (9)
CBRBHB	0	12 (4)	.9	–	3 (9)	9 (3)
Fibrinogen			.04			
<305 mg/dL	2 (9)	106 (35)	–	–	6 (17)	102 (35)
305-374 mg/dL	9 (39)	98 (32)	.05	4.7 (1.01-22)	6 (17)	101 (35)
≥375 mg/dL	12 (52)	98 (32)	.01	6.8 (1.5-31)	24 (67)	86 (30)

AHT indicates arterial hypertension; Peripheral a., peripheral arteriopathy; AMI, acute myocardial infarction; CCI, congestive cardiac insufficiency; 95% CI, 95% confidence interval. Fifteen patients were excluded from ECG analysis as they could not be interpreted (pacemaker rhythm, etc.).
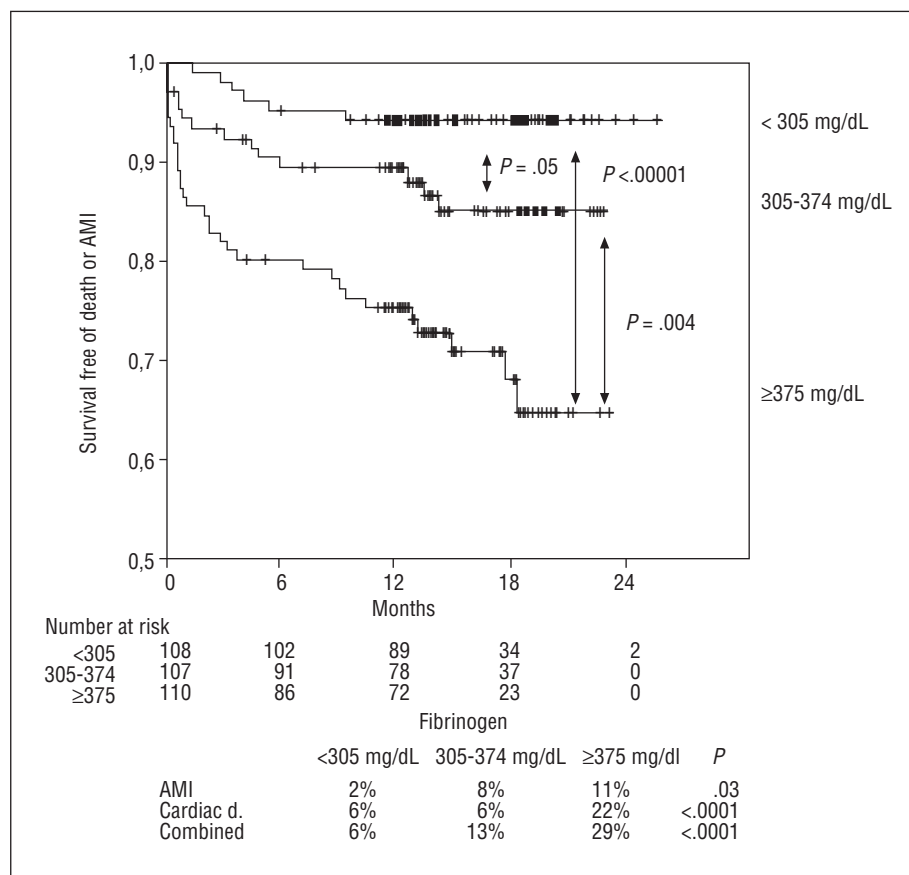

Fig. 1. Events at followup and fibrinogen value. Combined indicates cardiac death and infarct, or both. P (χ^2).

Univariate analysis

Cardiac death		Combined event			
P	HR (95% CI)	Yes (n=52)	No (n=272)	P	HR (95% CI)
<.00001	1.09 (1.05-1.13)	71±9	64±11	<.00001	1.07 (1.04-1.13)
0.7	1.1 (0.6-2.3)	17 (33)	73 (27)	.4	1.3 (0.7-2.3)
.0003	3.4 (1.8-6.6)	28 (54)	70 (26)	.0001	2.9 (1.7-5.1)
.4	0.7 (0.4-1.4)	24 (47)	149 (55)	.4	0.8 (0.4-1.4)
.03	2 (1.1-4.3)	31 (60)	127 (46)	.09	1.6 (0.9-2.8)
.02	0.3 (0.08-0.8)	8 (16)	77 (28)	.07	0.5 (0.2-1.1)
<.00001	5.1 (2.5-10.2)	20 (45)	39 (16)	<.00001	3.4 (1.9-6.2)
.001	5.4 (1.9-15.3)	44 (85)	155 (57)	.0007	3.7 (1.7-7.8)
.004	2.6 (1.4-5.1)	26 (50)	93 (34)	.02	1.9 (1.1-3.2)
<.00001	0.3 (3.2-12.5)	29 (56)	51 (19)	.00001	4.5 (2.6-7.8)
.8	0.9 (0.3-2.8)	5 (10)	27 (10)	.9	0.9 (0.4-2.5)
.9	1.0 (0.3-3.2)	3 (6)	25 (9)	.5	0.7 (0.2-2.1)
.03				.0009	
–	–	8 (16)	81 (31)	–	–
.8	1.1 (0.4-3.5)	7 (14)	75 (29)	.9	0.9 (0.3-2.7)
.02	2.9 (1.2-7.4)	29 (59)	73 (28)	.001	3.6 (1.6-7.8)
.6	0.5 (0.1-4.6)	2 (4)	23 (9)	.8	0.8 (0.2-3.9)
.05	3.9 (0.99-16)	3 (6)	9 (3)	.1	2.9 (0.8-11)
.0002				<.00001	
–	–	6 (11)	102 (37)	–	–
.9	1.0 (0.3-3.2)	14 (27)	93 (34)	.06	2.5 (0.96-6.5)
.001	4.4 (1.8-11)	32 (61)	78 (29)	<.00001	6.1 (2.6-14)

CAP, coronary angioplasty; CBRBHB, complete block of the right branch of the His bundle; Revascularization, CAP or previous heart surgery; HR, hazard ratio; Statistical analysis by univariate Cox regression analysis.

sion of monocytes and T lymphocytes to the endothelial surface, and on the conversely the liberation of various cytokines by both the endothelial cells and leukocytes. Said cytokines, basically interleukine (IL) 6,[9] stimulate hepatic synthesis of acute phase reactive proteins (such as PCR, serum amyloid A, or fibrinogen), all of which are sensitive but nonspecific markers of the inflammatory substrate. Fibrinogen is a protein that is directly implicated in the coagulation cascade, causing formation of fibrin 12; it is a key molecule in plaque aggregation[18] as it acts as a link between the plaque glycoproteins (GP) IIb-IIIa and improves conditioning of plasma

TABLE 5. **Association between clinical variables and the appearance of a combined event. Multivariate model**

	HR	95% CI	P
Age	1.05	1.01-1.08	.002
Previous angina	3.5	1.7-7.6	.004
ST decrease	2.6	1.5-4.5	.0009
Fibrinogen			.004
Middle tercil*	1.9	0.7-5.1	.2
Upper tertile*	3.8	1.6-9.2	.003

Statistical analysis was performed by Cox multivariate regression analysis. HR indicates hazard ratio; 95% CI, 95% confidence interval. The ECG variable was recalibrated for presence vs absence of decrease in ST segment. *Designates lower tertile.

viscosity, which has been related to a greater number of events in patients with ACS.[19]

Fibrinogen has been shown to be a cardiovascular risk factor in several epidemiological studies.[20-24] Similarly, fibrinogen values are elevated in patients with ischemic cardiopathy compared with healthy control subjects, with a decline according to whether Q AMI, non-Q AMI, unstable angina, or stable angina are involved.[25-27] In our patients, fibrinogen was significantly greater in the non-Q AMI group (377±88 mg/dL; average, 366) with respect to those with unstable angina (345±91 mg/dL; average, 338) (P=.02). These differences could not be attributed to a response to the acute phase induced by necrosis, as the initial detection of CPK on admission was similar in both.

The predictive value of clinical events, of fibrinogen and PCR values, in patients admitted with ACS has been evaluated with regard to short- and long-term in various studies. The results have been disparate, which has resulted in different recommendations from different research groups. On one hand, in the guidelines of the Spanish Society of Cardiology,[28] these markers of inflammation are not considered in ranking patient risk. The European Task Force[4] makes special mention of the value of both fibrinogen and PCR as markers for risk of events, death, or AMI during followup. In their final recommendations, only PCR, not fibrinogen, is included as a biological marker for assessing

long-term risk and is giving an evidence level of type A. Finally, in the ACC/AHA guidelines,[3] reactive protein C and other inflammation markers constitute type B (Class IIb) evidence for evaluating early risk without mention of its possible long-term value.

Several studies have analyzed the value of fibrinogen with respect to the appearance of short-term events. Elevated values of fibrinogen in patients admitted for unstable angina are associated with a greater incidence of refractory angina,[29] as well as death and severe arrythmias,[26] or both, during hospital stay. Becker et al,[27] in a TIMI IIIB (Thrombolysis In Myocardial Ischemia) sub-study that included 1,473 patients with unstable angina or non-Q AMI, showed that elevated fibrinogen values are related to a greater rate of recurrent ischemia and recurrent combined AMI-death-ischemia at 10 and 42 days of followup, with differences being significant only in the subgroup of patients with unstable angina and not in those with non-Q AMI. Nevertheless, there were no differences when AMI, death, or the combination of death or infarct was studied alone.

The association of markers for inflammation with the appearance of cardiac events long-term has also been evaluated. The ECAT (European Concerted Action on Thrombosis) Disabilities Angina Pectoris Study[30] included 2806 patients with ischemic cardiopathy who were about to undergo coronary angiography (48% with unstable angina), and considered to be AMI events (fatal or not) and sudden cardiac death. The fibrinogen values were greater in patients with an event during medium-term follow-up of 2 years (328 vs 300 mg/dL; $P=.01$), with the cut-off point for fibrinogen distribution of <271 mg/dL for the lower tertile and >331 for the upper tertile. The authors concluded that elevated fibrinogen levels, including the range that is considered normal, could be predictors of cardiovascular risk in patients with manifest heart disease.

Biasucci et al[10] performed a 1-year followup in 53 patients admitted with a diagnosis of grade IIB Braunwald angina, evaluated during this time re-admission due to angina or AMI. They analyzed the rate of episodes according to fibrinogen and PCR values, dividing the values into tertiles in both cases. The cut-off points for PCR were and 2.5 mg/dL (lower tertile, 13% of events); between 2.5 and 8.6 mg/dL (middle tertile, 42% of events); and 8.7 mg/dL (upper tertile, 67% of events). It was similar for fibrinogen, 300 mg/dL (22% of events); between 301 and 384 mg/dL (44% of events); and 385 mg/dL (59% of events). The cut-off points in tertiles for this study were practically interchangeable with ours. The differences were only significant for PCR, in both cases a growing progression in the rate of events, similar from the clinical point of view for both markers and similar to that we encountered. The inclusion in this study of re-admission due to angina justified the greater frequency of developed events.

Toss et al,[11] in a FRISC (Fragmin During Instability in Coronary Artery Disease) sub-study analyzed the predictive value of fibrinogen and PCR values at 5-month follow-up in 965 patients admitted by for unstable angina or non-Q AMI. A significant growing progression was noted in the rate of events for both cardiac death (1.6%, 4.6%, and 6.9%) as the combination of death or AMI (9.3%, 14.2%, and 19.1%), similar to that observed in our study, passing from the lower tertile to the upper tertile in fibrinogen distribution, with cut-off points for the lower tertile of 338 mg/dl and for the upper tertile 400 mg/dL, somewhat higher than ours. PCR was a predictor of death, with an event rate by tertile similar to fibrinogen (<2 mg/dL, 2.2%; 2-10 mg/dL, 3.6%; >10 mg/dL, 7.5%). Nevertheless, it was not a predictor of combined episodes. As demonstrated in previous studies, there was a clear correlation between the fibrinogen values and PCR (r=0.45; $P<.001$).

The same authors later published an extension of the study with a medium followup of 37 months.[13] Rate of cardiac death was 5.7%, 7.8%, and 16.5% in the respective tertiles of PCR, with the significant differences centering between the upper tertile and the rest. With respect to the fibrinogen tertiles, the event rate was 5.4%, 12%, and 12.9%, with significant differences between the lower tertile and the remainder. Therefore, while for fibrinogen the values in the middle tertile already represented an increased risk, said cut-off point for PCR was given with higher values.

Similar to our studies, ECG results on admission–especially changes in the ST segment or the presence of CBRBHB–have proven to be markers of eventual decline (death or non-fatal AMI) during followup,[31,32] and advanced age, previous angina, diabetes mellitus, and cardiac insufficiency on admission were also factors associated with a greater incidence of death in the progression.[33,34]

Hospital mortality was 3%, similar to that described by other authors.[2,35] During progression, the prognosis continued to be adverse, with an additional mortality of 8%, so that any attempt to rank the patients could result in a lower incidence of progressive episodes.

Limitations

In this study, neither the existence of proven ischemia on admission nor previously documented heart disease was included as criteria in this study. This could raise doubts as to whether the patients included in the study really had acute ischemic syndromes. Most studies include patients with electrocardiographic changes, positive troponin values, with AMI or prior heart disease (stenosis >70% on angiography). Without doubt, this would offer a higher level of confidence

that the patients included in the study really suffered had an ACS. Nevertheless, this also means that the inclusion criteria (selection bias) included subgroups of patients with an already known worse progression as determined in previous studies. Our patients were included if the original clinical diagnosis of unstable angina was maintained during their hospital stay and at discharge. We believe that in this manner a wider spectrum of initial admission diagnoses of unstable angina were included, which is more parallel with daily practice. In any case, our series documents evidence of ischemic cardiopathy, either by history or as revealed by tests performed during admission (non-invasive or coronary angiography) in 92% of cases. Of the remaining 26 patients, 9 were re-admitted for angina, constituting objective signs of ischemia. Therefore, it was not possible in only 5% of patients to prove any sign that was clearly indicative of ischemic cardiopathy, whether because of age and/or because the associated pathology was the reason for more conservative treatment, or because the non-invasive test results categorized the patient as low-risk and further tests were not performed. We believe, therefore, that our patients are representative of a broad range of people who appear to have unstable angina.

Each of the studies has a slightly different distribution of fibrinogen values, which is indicated by the distinct cut-off points in the classification into tertiles. This has made comparison between them and the extrapolation of results difficult. Nevertheless, all results point to the same conclusion: greater fibrinogen equals a greater number of progressive events.

CONCLUSIONS

Problems arise when an attempt is made to understand the significance and the value of fibrinogen levels in the individual patient. Our opinion is that at the moment fibrinogen levels should be just one piece of information in the evaluation of patient risk.

In our series, advanced age, elevated fibrinogen levels, a history of angina, and a decrease in ST segment evident on admission ECG are associated with a worse prognosis with a greater rate of cardiovascular episodes. The percentage of combined episodes progressed (6%, 13%, and 29%) with progression from the lowest to the highest tertile in fibrinogen distribution.

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