Fibrinogen as a predictor of mortality after acute myocardial infarction: a forty-two-month follow-up study

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Fibrinogen; Follow-up; Mortality; Myocardial infarction.

Background. **Several studies suggest that fibrinogen may be considered an independent risk factor for coronary artery disease, but it is still on debate if we need its evaluation during an acute myocardial infarction (AMI) to prevent future fatal or non-fatal cardiovascular events. Therefore, we decided to investigate this field.**

Methods. **We studied 92 male patients with AMI, evaluating at admission age, body mass index, systolic blood pressure, cigarette smoking, ejection fraction, plasma levels of total cholesterol, triglycerides, fibrinogen, glycemia, and white blood cell count. All patients were followed up for 42 months to evaluate total mortality and cardiovascular morbidity.**

Results. **During the follow-up 5 patients died and 64 had one or more non-fatal cardiovascular events: angina (n = 78), heart failure (n = 17), re-AMI (n = 3), stroke (n = 3), or revascularization procedure (n = 16). A multivariate analysis revealed that fibrinogen plasma levels at admission (r = +0.213, p < 0.05) were independently associated with mortality, while systemic thrombolysis was negatively associated (r = -0.447, p < 0.0001).**

Conclusions. **Plasma fibrinogen levels were the only independent predictor of mortality in a 42-month follow-up post-AMI. This finding, together with other observations from recent studies, suggest that fibrinogen evaluation during AMI may be useful in identifying patients at higher risk of acute event recurrence.**

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Introduction

Atherosclerosis is still a high-cost disease (in terms of drug therapies, rehospitalizations and revascularization procedures) in western countries and its clinical complications, such as acute myocardial infarction (AMI), represent in these populations a major cause of mortality[1]. In the last decades a number of studies showed the effective cost-benefit ratio of interventional approaches on the so-called "traditional" risk factors for coronary artery disease, with significant reductions in both cardiovascular morbidity and mortality[2,3]. However, the absence of the aforementioned risk factors do not totally protect from the disease.

Thus, it has been recently tried worldwide to identify "new" possible atherosclerosis risk factors, including biochemical factors and genetic polymorphisms[4]. Out of them, several studies suggested that high concentrations of fibrinogen may represent a strong risk factor for cardiovascular diseases[5-10], and, namely, for AMI[11-16] and coronary atherosclerosis progression[17-27]. However, it is still on debate whether or not we need the evaluation of its plasma concentrations during an AMI, in order to predict future fatal or non-fatal cardiovascular events[28-30]. Therefore, the aim of the present study was to evaluate, in a group of patients with AMI, the possible predictive role of plasma fibrinogen levels on cardiovascular morbidity and total mortality in a 42-month follow-up study.

Methods

We studied a group of 150 male patients admitted consecutively to an intensive care unit for AMI within 6 hours of the appearance of cardiac symptoms. The diagnosis of AMI was performed in presence

of at least one of the following criteria: 1) typical chest pain; 2) upsloping or downsloping of the ST segment ≥ 2 mm in two precordial leads or ≥ 1 mm in a peripheral lead, with a concomitant at least 2-fold elevation of myocardial necrosis enzymes (creatine phosphokinase and creatine kinase-MB). Patients > 75 years (n = 37), receiving oral anticoagulants (n = 7), suffering from other acute or chronic inflammatory diseases (2 rheumatoid arthritis, 2 psoriatic arthritis, 1 acute pneumonia) or peripheral vascular diseases (n = 9), were excluded from the study in order to avoid potential bias source, eventually including a total number of 92 patients.

We recorded patient's characteristics (sex, age, weight, height, smoking habit), clinical variables like ventricular ectopic beats, ejection fraction, systolic blood pressure, heart rate and the baseline laboratory analysis (total cholesterol, triglycerides, fibrinogen, glycemia, white blood cells) from the first blood sample obtained at admission, before any pharmacological therapy, thus during the 24-hour period. Venous blood samples were obtained by separate puncture from an antecubital vein, collected with minimal venous stasis into 0.106 M trisodium citrate and then centrifuged for 10 min. Fibrinogen determination was rapidly performed according to the Clauss coagulative method, being the normal range of our laboratory between 200 and 350 mg/dl. All the other laboratory analyses were performed by standard procedures. The body mass index was obtained by the formula kg/m^2

All patients were followed for 42 months, in five evolving stages, at 6, 12, 18, 30 and 42 months. At each step we measured fibrinogen levels and white blood cell count, recording total mortality and several cardiovascular adverse events, which included recurrent angina, heart failure, paroxysmal atrial fibrillation episodes, re-AMI, stroke, and revascularization procedures, e.g. percutaneous coronary intervention or coronary artery bypass graft.

Statistical analyses were performed using the Statview Program (Abacus Concepts Inc., USA). Means and SDs were calculated and the differences were analyzed using the Student's t-test. Statistical significance was considered to be achieved when differences between groups had p values < 0.05. Multiple regression analysis was performed using a stepwise model, to identify possible variables independently correlated with mortality in the follow-up. Due to the low number of fatal events, we also tested the differences between the groups using the Mann-Whitney non-parametric test.

Results

Table I shows the patients' clinical and laboratory characteristics at admission. Regarding the traditional cardiovascular risk factors, we found a low prevalence of obesity, diabetes mellitus, chronic renal failure and hypertension, but the smoking habit was noticeably present. The ejection fraction was not much impaired. The heart rate was normal.

Table I. Patient's clinical and laboratory characteristics at baseline.

Clinical variables	
Age (years)	56 ± 9
BMI (kg/m^2)	27 ± 4
Obesity (BMI > 30 kg/m^2) (%)	17
Chronic renal failure (%)	7.6
Hypertension (%)*	14
Diabetes mellitus (%)	14
Cigarette smoking (%)	88
No. cigarettes	23 ± 12
Ejection fraction (%)	51 ± 11
Heart rate (b/min)	63 ± 7
VEBs/hour > 5 (%)	13
Plasma laboratory variables	
Total cholesterol (mg/dl)	210 ± 34
Triglycerides (mg/dl)	165 ± 75
HDL cholesterol (mg/dl)	41.3 ± 10
LDL cholesterol (mg/dl)	139 ± 34
Fibrinogen (mg/dl)	505 ± 194
Glycemia (mg/dl)	93 ± 25
Creatinine (mg/dl)	1.19 ± 0.48
White blood cells (× 10^3 ml)	7800 ± 1900
Neutrophils (%)	59 ± 7
Lymphocytes (%)	28 ± 7
Monocytes (%)	8 ± 3

BMI = body mass index; VEBs = ventricular ectopic beats. * blood pressure > 140/90 mmHg.

At the admission ECG 60 patients showed upsloping of the ST segment, while 32 downsloping. A Q wave AMI has been observed in 58 cases (the anterior wall was interested in 31 cases, the inferior in 27), while a non-Q wave AMI in 34 (the anterior wall in 23, the inferior in 11). Forty-eight patients were treated by systemic thrombolysis, 26 with streptokinase and 22 with recombinant tissue-type plasminogen activator. At discharge patients received respectively treatments with antiplatelet drugs (98.9%), beta-blockers (76.1%), angiotensin-converting enzyme inhibitors (45.7%), nitrates (94.6%), calcium channel blockers (23.9%), diuretics (20.6%), and statins (31.5%).

Regarding the laboratory patterns (Table I), patients showed normal ranges in both plasma glycemia and lipids. We found, in contrast, increased levels of leukocytes together with considerable high levels of plasma fibrinogen (505 ± 194 mg/dl).

To determine if alterations in fibrinogen levels or in the leukocyte formula may have been due to an acute phase response post-AMI, these two parameters were evaluated during the whole follow-up period (Table II). Both plasma concentrations of fibrinogen and of white cells significantly decreased already 6 months after the acute event and continued to decrease until the end of the follow-up. The relative concentrations of neutrophils did not show any significant change (with ex-

Table II. Plasma laboratory variables during the follow-up.

Variables	Admission	6 months	12 months	18 months	30 months	42 months
Fibrinogen (mg/dl)	505 ± 194	391 ± 126*	355 ± 102*	338 ± 92*	332 ± 102*	305 ± 84*
WBC ($\times 10^3$ ml)	7800 ± 1900	6700 ± 1600*	6700 ± 1500*	6900 ± 1600*	7000 ± 1600*	6500 ± 1700*
Neutrophils (%)	59 ± 7	57 ± 7	56 ± 6**	56 ± 8	57 ± 7	57 ± 7
Lymphocytes (%)	28 ± 7	31 ± 7**	31 ± 6§	32 ± 8§	32 ± 7§	31 ± 7**
Monocytes (%)	8 ± 3	7 ± 2**	6 ± 2**	7 ± 2**	7 ± 2**	7 ± 2**

WBC = white blood cells. * $p < 0.0001$, ** $p < 0.05$, § $p < 0.001$, vs admission.

ception of a slight decrease at 12 months), while lymphocytes increased and monocytes decreased.

Figure 1 evaluates the severity of coronary disease showing the number of affected coronary vessels as results of coronary arteriography.

In table III we report the adverse cardiovascular events registered during the follow-up. The total events were 123, occurring in the 73% of patients (some patients had more than one adverse event during the follow-up). Almost half of the total events occurred 6 months after AMI and angina was overall the most frequent event (78 total episodes). We also registered 17 heart failure episodes, 16 revascularization procedures (10 coronary artery bypass grafts and 6 percutaneous coronary interventions), 3 cerebrovascular ischemia episodes, 3 re-AMI, and one episode of paroxysmal atrial fibrillation. Five patients died during the follow-up, 3 for AMI, 1 for chronic heart failure, and 1 for liver cirrhoses (this patient was not included in the statistical analyses).

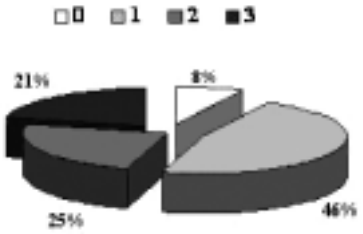

Figure 1. *Coronary arteriography results: number of affected vessels.*

Figure 2 shows the relationship between fibrinogen plasma levels and adverse events; as expected, we registered, in patients with high plasma levels of fibrinogen at admission (≥ 350 mg%), a higher prevalence of adverse events during the follow-up.

To evaluate if the adverse events were related to the baseline fibrinogen levels, we performed a univariate statistical analysis (Table IV), and results showed that patients who died during the follow-up presented higher levels of fibrinogen at baseline. We did not find any significant difference in fibrinogen basal levels in patients with different adverse events, with the exception of those with angina episodes during the recovery and 6 months after AMI.

Table V shows the clinical and biochemical parameters in patients who died during the follow-up, in relation to the survivors. In addition to the findings regarding fibrinogen we found that patients with a fatal event presented a significantly higher body mass index value and increased concentration of plasma glycemia in relation to the survivors. Other differences, such as the older age, the higher prevalence of hypertension, the lower ejection fraction and the higher prevalence of ventricular ectopic beats, were not statistically significant. Using the Mann-Whitney non-parametric test, fibrinogen was the only variable that maintained the statistical significance ($p < 0.05$); in particular the highest values of fibrinogen were measured in patients with fatal events during follow-up.

We also built up a multivariate analysis, including the clinical and biochemical variables evaluated at admission; in this analysis fibrinogen was the only vari-

Table III. Adverse events registered during the follow-up*.

	6 months	12 months	18 months	30 months	42 months	Total
Total adverse events	52	16	17	15	23	123
Angina	37	12	9	9	11	78
Heart failure	3	2	4	4	4	17
Paroxysmal atrial fibrillation	0	0	0	0	1	1
Reinfarction	0	1	1	1	0	3
Stroke	0	1	0	0	2	3
CABG	7	0	2	0	1	10
PCI	5	0	0	1	0	6
Death	0	0	1	0	4	5

CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention. * in some patients more than one adverse event was registered during the follow-up; only 23 patients were free of events.

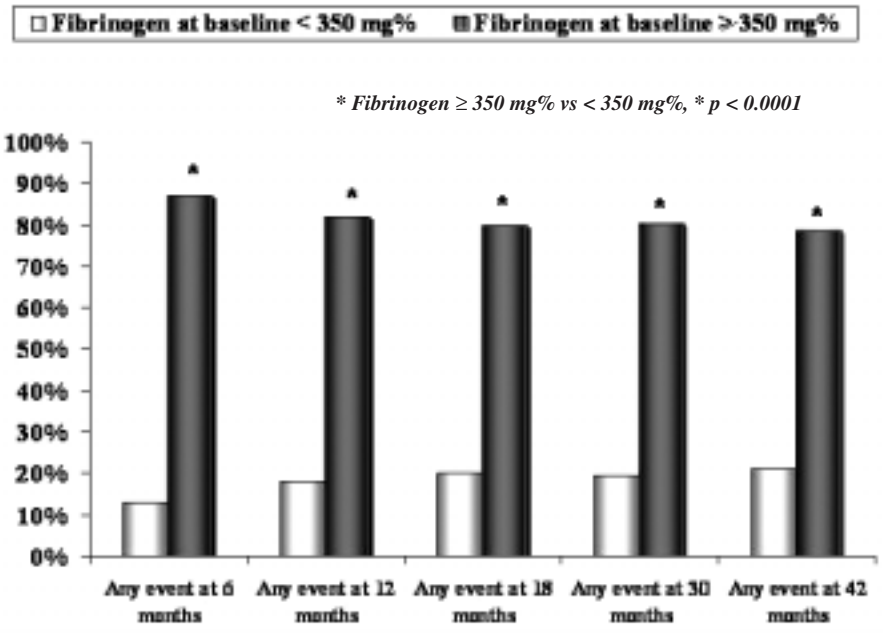

Figure 2. *Relationship between fibrinogen plasma levels and adverse events.*

Table IV. Plasma levels of fibrinogen in patients with vs patients without adverse events during follow-up.

Variables	Patients with (mg/dl)	p	Patients without (μmg/dl)
Any adverse event	509 ± 200	NS	501 ± 184
Fatal events	706 ± 176	< 0.05	495 ± 191
Any event at 6 months	515 ± 209	NS	493 ± 172
Any event at 12 months	530 ± 233	NS	496 ± 187
Any event at 18 months	586 ± 235	NS	491 ± 184
Any event at 30 months	493 ± 199	NS	506 ± 196
Any event at 42 months	556 ± 206	NS	491 ± 192
Angina	555 ± 200	< 0.05	455 ± 178
Heart failure	524 ± 285	NS	505 ± 185
Reinfarction	576 ± 364	NS	504 ± 190
Stroke	584 ± 368	NS	504 ± 190
CABG	513 ± 210	NS	505 ± 193
PCI	456 ± 142	NS	510 ± 199
Angina at 6 months	570 ± 203	< 0.05	463 ± 179

CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

able independently associated with mortality (r = +0.181, p < 0.05), while systemic thrombolysis was negatively associated (r = -0.447, p < 0.0001) (Table VI).

Discussion

Our study considered fibrinogen plasma levels in patients with AMI and their time pattern in a 42-month follow-up, in order to evaluate their role as risk factors predictive of new cardiovascular events after the acute phase.

Experimental evidence showed that fibrinogen, a 340 kD glycoprotein synthesized by the liver, is early involved in the formation and growth of atheroma infiltrating the arterial wall, and it is also the precursor of mural fibrin thrombi, later incorporated into the arterial wall. Within it, fibrin binds other coagulative factors and oxidized low-density lipoproteins, and it is converted into degradation products, then stimulating smooth muscle cells migration and proliferation, as well as the uptake of lipids by macrophages[5,31,32]. Recently it has been demonstrated that plasma fibrinogen is significantly associated

Table V. Baseline clinical data and laboratory values in patients with or without fatal events in the follow-up.

Variables	Patients without (n=87)	p	Patients with (n=4)*
Age (years)	56 ± 9	NS	64 ± 9
Body mass index (kg/m^2)	27 ± 3	< 0.05	31 ± 6
Hypertension (%)	14	NS	20
Diabetes mellitus (%)	18	–	–
Cigarette smoking (%)	88	NS	80
Chronic renal failure (%)	6	NS	20
Q AMI (%)	62	NS	60
Non-Q AMI (%)	38	NS	40
Three-vessel disease (%)	18	NS	20
Anterior wall AMI (%)	64	NS	80
Inferior wall AMI (%)	36	NS	20
Ejection fraction (%)	52 ± 11	NS	45 ± 12
Heart rate (b/min)	63 ± 7	NS	60 ± 11
VEBs/hour > 5 (%)	13	NS	20
Creatinine	1.15 ± 0.22	NS	1.32 ± 0.7
Total cholesterol (mg/dl)	209 ± 34	NS	218 ± 33
Triglycerides (mg/dl)	164 ± 73	NS	188 ± 114
Glycemia (mg/dl)	91 ± 22	< 0.01	123 ± 51
Fibrinogen (mg/dl)	495 ± 191	< 0.05	706 ± 176
Fibrinogen ≥ 350 mg%	77	< 0.00005	100
White blood cells ($\times 10^3$ ml)	7800 ± 1800	NS	6500 ± 3100
Neutrophils (%)	59 ± 7	NS	55 ± 11
Lymphocytes (%)	28 ± 6	NS	29 ± 12
Monocytes (%)	7 ± 3	NS	10 ± 5

AMI = acute myocardial infarction; VEBs = ventricular ectopic beats. * one patient died of liver cirrhosis and was not included in the statistical analyses.

Table VI. Multiple regression analysis: fatal events vs 9 independent variables.

	r	p
Fibrinogen (≥ 350 mg%) at admission	+0.181	< 0.05
Systemic thrombolysis	-0.447	< 0.0001

Variables not included in the analysis (p > 0.05): age, body mass index, cigarette smoking, ventricular ectopic beats/hour, hypertension, diabetes, non-Q/Q wave myocardial infarction, anterior/inferior myocardial infarction, single/multivessel disease, chronic renal failure, total cholesterol, triglycerides, glycemia, white blood cell count at admission.

with a high quantity of coronary artery calcifications, a marker of preclinical coronary atherosclerosis[33]. Fibrinogen is also involved in a number of mechanisms (endothelial cell injury, platelet aggregation, and plasma viscosity) that play a central role in the formation of thrombi: first, it is an important determinant of platelet aggregation, binding to the platelet membrane glycoprotein receptor IIb/IIIa; second, having fibrinogen a crucial role in the coagulative process, since it represents the physiological substrate of thrombin, hyperfibrinogenemia may induce a hypercoagulative state by a procoagulant imbalance, leading to the formation of insoluble fibrin[31,32]; third, fibrinogen, due to its form of large and elongated molecule and to its binding capacity, is the major determinant of blood viscosity, decreasing microcirculatory blood flow and capillary blood flow velocity, thus favoring leukocyte and red blood cell adhesion with consequent microvascular ischemia.

The importance of hyperfibrinogenemia as a risk factor for atherothrombosis is confirmed by a number of previous studies showing an association between high fibrinogen levels and a) other risk factors for cardiovascular disease, including age, smoking habit, cholesterol, physical inactivity, arterial hypertension, and diabetes[6,15,34], b) angiographically determined number and severity of coronary and extracoronary stenosis[6,7,15,35], and c) future risk of cardiovascular events such as angina pectoris, myocardial infarction, stroke and sudden death[5-10,17-27]. The meta-analysis of Maresca et al.[23] demonstrated that the estimated risk of coronary artery disease is more than doubled when comparing the higher tertile of fibrinogenemia with the lower one.

Less data are known about the predictive long-term value of fibrinogen levels obtained early in the acute phase of a myocardial infarction. Fibrinogen levels higher than the median values (371 mg/dl) as well as leukocytes, determined at discharge, are essential part of cardiovascular risk in the GISSI-Prevenzione mortality risk chart[36]. In contrast, in patients with acute coronary syndromes Choussat et al.[37] failed to demonstrate that fibrinogen levels are predictive of coronary events during follow-up and, in myocardial infarction

survivors, in whom blood sample was determined also at hospital discharge, only C-reactive protein (CRP) and leukocyte count, but not fibrinogen, show a relationship with future cardiovascular events[38].

Our study was performed in 92 male patients, consecutively admitted to a coronary intensive care unit for AMI, and followed up along a period of 42 months. Our population had a basal low-moderate risk, as they were not of older age and presented a low prevalence of traditional risk factors (particularly hypertension, diabetes, hypercholesterolemia, and obesity), with the exception of a large prevalence in smoking habit. Entry fibrinogen levels were markedly elevated, according to other authors[33] and we noticed their progressive decrease during the follow-up. This significant reduction in fibrinogenemia, as well as in leukocyte number, observed already 6 months after the acute event, confirms the presence of an acute phase reaction, although in our study patients showed normal values of both plasma glycemia and lipids, lacking the frequent acute phase response post-AMI of lipid parameters[39], probably due to the precocious blood examination. However, the acute phase response does not fully explain the high fibrinogen levels in acute ischemic patients, as they are slightly elevated also in patients with chronic coronary heart disease when compared to control patients[7,11].

Although it is pathophysiologically conceivable that genetic variations in coagulation proteins are associated with the risk of myocardial infarction, recent data show that association between polymorphisms in fibrinogen 455A allele and myocardial infarction is weak or absent[40]; in contrast, since atherosclerosis reveals certain similarities to inflammatory diseases, hyperfibrinogenemia in patients with intracoronary obstructive lesions might be partly reactive to a chronic inflammatory process. Recent studies have in fact demonstrated that patients with chronic infections have a greater prevalence in ischemic heart diseases[37,41]. Infectious agents could play a role by increasing the release of cytokines, whose role in fibrinogen synthesis is well known (being its expression regulated by interleukin-6). Thus fibrinogen may be an actor in an immune and inflammatory response, involving endothelial and smooth muscle cells, that accompanies the accumulation of lipids and fibrous materials in the atheromatous plaques, as well as its weakening and disruption that induces thrombosis[42].

The analysis of adverse events during the follow-up has revealed that basal fibrinogen levels are associated with recurrent angina episodes and with fatal events. Particularly, patients who died showed a significant prevalence of high levels of fibrinogen, diabetes and obesity than surviving ones. Other parameters, such as older age, arterial hypertension, and lower ejection fraction did not result statistically significant. Multivariate analysis has shown that the only variable associated independently with fatal events has been the fibrinogen levels. Thus, early fibrinogen levels at the onset of an AMI may be a marker of future adverse cardiac events, probably showing a greater susceptibility of these patients to immune and inflammatory processes involved in atherothrombosis.

Other acute phase reactants have recently been shown to have an independent short-term and possibly long-term prognostic value in acute coronary syndromes, such as CRP, alpha 1-acid glycoprotein and interleukin-6[42,43]; thus, a limitation of this study is the lack of data on these factors and, above all, on CRP, that may account for half of the variance in plasma fibrinogen concentrations[15]. Actually, Reganon et al.[29] demonstrated that, even 5 years after a myocardial infarction, there is clear evidence of low-grade inflammation, with increased plasma fibrinogen levels related to sialic acid and CRP, that was accompanied by fibrin formation and thrombin generation. Thus, it seems useful to perform further studies using concomitant data on fibrinogen and other acute phase proteins, such as CRP, interleukin-6, or CD4 ligand. Concordance of their time patterns over a long-term follow-up would enhance their value and identify a panel of useful biochemical parameters able to individuate a high-risk subgroup of patients.

Another possible limitation of the study is that, as the blood samples were obtained at entry, results might have been influenced by the circadian rhythm of fibrinogen[43]. On the other hand, execution of blood samples at a single hour range might have determined greater bias, due the possible too long distance of the sampling from the moment of necrosis occurrence.

In conclusion, our data, linking early basal levels of fibrinogen in patients with an AMI and future fatal events in a 42-month follow-up, support previous studies suggesting that fibrinogen has to be considered an independent risk factor for cardio- and cerebrovascular events[44]. Early fibrinogen dosage may be an easy, inexpensive and useful means in identifying the higher-risk subgroups in patients with AMI. Further investigations are needed to evaluate whether patients with ischemic heart disease may benefit from fibrinogen lowering with non-pharmacological measures or with new specific drugs. In particular, further demonstrations of the predictive value of fibrinogen may suggest, in presence of its high levels, a more aggressive approach even in the acute phase, i.e. by using glycoprotein IIb/IIIa inhibitors or urgent revascularization interventional techniques.

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