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Determinants of fibrinogen in an Italian population suffering from claudication. Lower fibrinogen in the south compared to middle and north of Italy

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ABSTRACT

Background and Objective. **Prospective studies have shown that high plasma levels of fibrinogen are independently associated with the risk of cardiovascular complications. In patients suffering from peripheral vascular disease (PVD) fibrinogen has been shown to be an independent predictor of cardiovascular disease but its determinants have never been examined in this clinical setting.**

Design and Methods. **Fibrinogen levels were related to clinical and laboratory variables in 2,111 patients suffering from PVD. We also analyzed whether there was a regional distribution of risk factors.**

Results. **The median values of fibrinogen was 312 mg/dL. The clinical variables examined did not differentiate patients with elevated or normal fibrinogen levels. In particular, patients with ankle/arm pressure ratio < 0.8 did not show a higher prevalence of fibrinogen > 312 mg/dL. Conversely, white blood cell (WBC) count and serum cholesterol levels were significantly associated with high fibrinogen levels ($p<0.0001$). Multiple logistic regression analysis demonstrated that areas of Italy were differently associated with high plasma fibrinogen levels ($p<0.03$): subjects in the north and middle of Italy having significantly higher values of fibrinogen than subjects in the south of Italy ($p<0.01$). A similar regional distribution was observed for WBC count and serum cholesterol levels.**

Interpretation and Conclusions. **The regional distribution of risk factors raises the question as to whether the already reported large variability of cardiovascular events so in PVD may be attributed to a non homogeneous distribution of risk factors.**

Key words: fibrinogen, peripheral vascular disease, Italian regions, risk factors

Several prospective studies provided evidence that a high fibrinogen level is an independent predictor of cardiovascular complications and that fibrinogen may play an important role in the pathogenesis of atherosclerosis.[1-5] In the setting of peripheral vascular disease (PVD), fibrinogen values have been reported to be increased and to predict the re-occlusion of femoro-popliteal vein grafts.[6] These data has been recently supported by a large trial performed in an Italian population suffering from claudication (ADEP study).[7] In this study, which included over 2,000 patients with PVD, plasma fibrinogen was shown to be an independent predictor of all cardiovascular events. Also, dividing the vascular events according to the circulatory area, plasma fibrinogen was shown to predict in particular cerebro-vascular events such as stroke and transient ischemic attacks.[8]

Several factors may influence plasma fibrinogen; they include age, alcohol consumption, social class, obesity, serum cholesterol, diabetes mellitus, smoking, white cell count.[5] It is plausible that the above reported determinants are also important in patients with PVD, but, until now, data exploring this particular issue are not available.

We took advantage of the availability of data deriving from the ADEP study to retrospectively investigate whether or not the determinants of fibrinogen in PVD are similar to those previously reported. Also, since the Italian centers were *a priori* selected in the north, middle and south of Italy, we investigated whether there was a regional difference in the distribution of fibrinogen as well as other risk factors for atherosclerosis.

Materials and Methods

Subjects

The present study was carried out in patients suffering from PVD enrolled in an Italian double blind, randomized, multicenter trial, stratified by center, planned to assess the therapeutic effect of picotamide.[9,10] All patients were recruited between January 1989 and August 1989 as reported elsewhere.[7] One hundred and twenty Italian centers participated in the study. The enrollment of patients started on January 1st, 1989, and closed on August 30th, 1989. During this period, 2,304 patients were recruited. During the study, 116 patients were lost to follow-up and 77 were withdrawn from the trial because of side effects. Therefore, the on-treatment group was com-

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posed of 2,111 PVD patients (347 females and 1,764 males, aged from 40 to 78 years).

Study design and methods

Several factors known to influence fibrinogen levels[5] were considered in this study; in addition all the risk factors for the cardiovascular complications in PVD patients were included as possible determinants of high fibrinogen levels.[8] All the factors considered are listed in the rest of the paragraph.

Smokers were defined as patients smoking at least five cigarettes a day. Hypertension was defined as a blood pressure higher than 140/90 mmHg measured on at least 2 different days while the patient was at rest for at least 10 min. Patients with a blood pressure lower than the cut-off point but on medical therapy for hypertension were also considered hypertensives. Diabetes was defined as the use of insulin or oral hypoglycemic drugs. A positive history of vascular surgery was when the patient has had an endarterectomy, aorto-coronary bypass, angioplasty, femoro-iliac or femoro-popliteal bypass or peripheral angioplasty. Ankle/arm pressure ratio was defined as abnormal if less than 0.8.[8]

During the randomization phase and throughout the follow-up, which lasted 18 months, many meetings were carried out between the researchers participating in the study. In order to facilitate the meetings it was decided *a priori* that researchers from the centers in the north (Piemonte, Valle d'Aosta, Lombardia, Liguria, Veneto, Trentino, Friuli), middle (Toscana, Emilia Romagna, Abruzzo, Marche, Umbria, Lazio) and south (Puglia, Sardegna, Campania, Sicilia, Calabria) of Italy would meet separately. The rate of enrolment from January to August was equally distributed between the areas of Italy. The baseline laboratory findings were used for the statistical analysis. Blood samples were taken between 8.00 and 9.00 a.m. from patients who had fasted for at least 12h and sent for analysis to the local laboratory of each centre. The following variables were measured for each sample: white blood cell (WBC) count ($\times 10^9$ cells/L), hematocrit (%), cholesterolemia (mg/dL) and triglyceridemia (mg/dL). Fibrinogen plasma levels were measured by the Clauss method[11] in 95% of patients. Standardization of the laboratory data was performed as previously described.[8]

The major events taken into consideration during the ADEP study were: (a) vascular and non-vascular death, (b) fatal and non-fatal myocardial infarction (MI), (c) fatal and non-fatal stroke, (d) amputation above the ankle for reasons other than tumor or trauma, and (e) surgery for ischemic viscera. Minor events included: (a) recently developed angina or unstable angina, (b) possible or probable MI, (c) transient ischemic attacks (TIA), (d) minor stroke, (e) recently developed renal failure, (f) hypertension, and (g) deterioration of vascular disease leading to surgical intervention, angioplasty or local thrombolysis. The occurrence of any of the above minor events did not require treatment discontinuation. If a patient had both a minor and a major event, only the latter was counted; each patient contributed only one event.

Table 1. Clinical and laboratory characteristics of PVD patients divided according to fibrinogen levels.

	Patients with fibrinogen plasma levels ≤ 312 mg/dL (n=1110)	*p value*	*Patients with fibrinogen plasma levels >312 mg/dL (n=1001)*
Males			
n (%)	921 (83)	NS	843 (84)
Age (years) (range)	63±8 (40-78)	NS	63±7 (40-75)
Ankle/arm pressure ratio < 0.8			
n (%)	517 (47)	NS	504 (50)
Smoking			
n (%)	373 (34)	NS	344 (34)
Hypertension			
n (%)	380 (34)	NS	365 (36)
Diabetes			
n (%)	207 (19)	NS	190 (19)
High white blood cell count (> 7.0x10⁹ cells/L)			
n (%)	451 (41)	<0.0001	546 (55)
High hematocrit (>43.5%)			
n (%)	536 (48)	NS	498 (50)
High total cholesterol (>220 mg/dL)			
n (%)	482 (43)	<0.0001	526 (53)
High triglycerides (>149 mg/dL)			
n (%)	536 (48)	NS	516 (52)
Italian region			
n (%)		<0.01*	
North	318 (29)		331 (33)
Middle	458 (41)		427 (43)
South	334 (30)		243 (24)

**p values refer to trends in proportions. The subdivision of the chi-square statistic is the following: north vs. middle, p>0.05; north vs. south, p<0.01; middle vs. south, p<0.02.*

Statistical analysis

Statistical analysis was performed by chi-square statistics and by ANOVA and appropriate multiple comparisons test. When necessary, log transformation was used to normalize the data, or appropriate non-parametric tests were employed. In particular, skewness in the distribution of fibrinogen (mean±SD: 329±89 mg/dL; range: 31-819 mg/dL) was diminished by truncation on the median value of the whole population (312 mg/dL). To determine the variables capable of being independently predictive of high fibrinogen values (more than 312 mg/dL) a multiple logistic regression analysis was done. The laboratory variables (such as: fibrinogen, total cholesterol, tryglicerides, WBC count, hematocrit) and age were

coded on the median value of whole series of patients. Italian areas were coded as north (including 7 Italian regions), middle (including 6 Italian regions) and south (including 5 Italian regions). Data are presented as mean±standard deviation. Only two-tailed probabilities were used for testing statistical significance. A p value < 0.05 was regarded as statistically significant.[12] All calculations were made using a personal computer software (Stat View II by Abacus Concepts, Berkeley, CA and EGRET by SERC, Seattle, Wash., USA).

Results

In the whole PVD population the median value of plasma fibrinogen was 312 mg/dL (mean±SD: 329±89 mg/dL); one thousand and one patients (47%) had fibrinogen values higher than 312 mg/dL. Table 1 reports the clinical and laboratory variables associated with high fibrinogen values. Sex, age, hypertension, smoking, diabetes and high hematocrit values did not differentiate patients with fibrinogen > or ≤ 312 mg/dL. The concentration of fibrinogen was not related to the severity of atherosclerosis. Thus, in patients with ankle/arm pressure ratio below 0.8, which identifies the patients with more severe PVD, we did not observe a higher prevalence of elevated values of fibrinogen.

Among the laboratory indices, high WBC count and serum cholesterol were significantly associated with high values of fibrinogen; 55% and 53% of patients with fibrinogen > 312 mg/dL also had high values of WBC count and serum cholesterol, respectively. Intriguingly, we also found a different distribution of fibrinogen values in the 3 areas of Italy. Thus, there was a significantly lower percentage (24%) of patients with high fibrinogen values in the south of Italy than in middle Italy (43%) and north of Italy (33%). Logistic regression analysis (Table 2) was used to model the relationship between the above mentioned variables and high fibrinogen levels. This analysis confirmed that high WBC count, high serum cholesterol and areas of Italy were independently related to high fibrinogen values. When the prognostic variables were used in a stepwise regression analysis we obtained similar results; in fact, the independent predictors of high plasma fibrinogen values were only high WBC count (coefficient = 0.53, SE = 0.09, OR = 1.70, 95% confidence limits = 1.42-2.02, p<0.001), high total cholesterol (coefficient = 0.30, SE = 0.09, OR = 1.35, 95% confidence limits = 1.13-1.61, p<0.001), and areas of Italy (coefficient = 0.13, SE = 0.06, OR = 1.14, 95% confidence limits = 1.0-1.28, p=0.029).

Table 2. Logistic regression analysis (full model) of high fibrinogen plasma values (>312 mg/dL) in the whole PVD series. Codes are 0 for No, 1 for Yes. Areas of Italy are coded as 0 for south, 1 for middle and 2 for north of Italy.

Determinant	*Regression coefficient (b)*	*Standard error se (b)*	*Odds ratio*	*95% confidence limits*	*p*
Constant	-0.81	0.16	0.4	0.3-0.6	<0.001
Male	0.07	0.12	1.1	0.8-1.4	NS
Hypertension	0.1	0.09	1.1	0.9 -1.3	NS
Smoking	-0.03	0.09	1.0	0.8-1.2	NS
Diabetes	0.04	0.11	1.0	0.8-1.3	NS
Index < 0.8	0.10	0.09	1.1	0.9-1.3	NS
Areas of Italy	0.12	0.06	1.13	1.0-1.3	=0.044
High WBC count	0.53	0.09	1.69	1.4-2.0	<0.001
High hematocrit	-0.02	0.09	1.0	0.8-1.2	NS
High total cholesterol	0.31	0.09	1.36	1.1-1.6	<0.001
High triglycerides	0.02	0.09	1.0	0.8-1.2	NS

The different distribution of fibrinogen values in the 3 areas of Italy prompted us to analyze further the clinical laboratory characteristics of the PVD populations in the south, middle and north of Italy (Table 3). We found a higher percentage of patients with severe atherosclerosis in north and middle Italy than in the south of Italy. Thus, in north and middle Italy, there was a higher prevalence of patients with ankle/arm pressure ratio <0.8 (north=56%, middle=50%, south=38%, p<0.0001) and previous vascular surgery (north=36%, middle=29%, south=19%, p<0.0001). Conversely, diabetes was significantly more prevalent in the south than north and middle Italy (p<0.001). Three laboratory variables demonstrated a clear regional distribution; plasma fibrinogen, WBC count and serum cholesterol levels. Thus, the prevalence of high values of fibrinogen, WBC count and serum cholesterol was significantly lower in the south than middle and north of Italy, with the exception of WBC count which was not significantly different between middle and south Italy (Table 3). Similar findings were obtained after excluding patients with more severe atherosclerosis. Thus, in patients without previous vascular surgery and ankle/arm pressure ratio >0.8 (n=808) we observed again that fibrinogen and serum cholesterol have a regional distribution with the lowest percentage of high values occurring in the south of Italy (Table 4); WBC count was higher in the north compared to middle and south but, again, there was no difference between middle and south Italy.

During 18 months of follow-up, 246 (12%) PVD patients had cardiovascular events. As shown in Table 5, in the south there was a significantly lower percentage of cardiovascular events than in the north or middle of Italy (p<0.02). After excluding patients without vascular surgery and ankle/arm pressure

Table 3. Regional distribution of clinical and laboratory characteristics of PVD patients.

		North (n=649)	*p value*	*Middle (n=885)*	*p value*	*South (n=577)*	*p value North vs. South*
Ankle/arm pressure ratio < 0.8 p<0.0001	n (%)	364 (56)	<0.002	440 (50)	<0.0001	217 (38)	<0.0001
Previous vascular surgery p<0.0001	n (%)	235 (36)	<0.002	254 (29)	<0.0001	112 (19)	<0.0001
Diabetes p<0.001	n (%)	141 (24)	NS	15 (17)	<0.001	105 (17)	<0.001
High fibrinogen (>312 mg/dL) p<0.01	n (%)	331 (51)	NS	427 (48)	<0.03	243 (42)	<0.002
High white blood cell count (>7.0×10^9 cells/L) p<0.001	n (%)	348 (54)	<0.001	392 (44)	NS	257 (45)	<0.002
High hematocrit (>43.5%) p<0.04	n (%)	336 (52)	<0.02	405 (46)	NS	293 (51)	NS
High total cholesterol (>220 mg/dL) p<0.0001	n (%)	372 (57)	<0.001	413 (47)	<0.003	223 (39)	<0.0023

Table 4. Regional distribution of clinical and laboratory characteristics of PVD patients without previous surgery and with an ankle-arm index more than 0.8.

		North (n=189)	*p value*	*Middle (n=323)*	*p value*	*South (n=296)*	*p value North vs. South*
Diabetes p<0.01	n (%)	75 (25)	NS	60 (19)	<0.01	27 (14)	NS
High fibrinogen (>312 mg/dL) p<0.02	n (%)	103 (54)	NS	150 (46)	NS	120 (41)	<0.01
High white blood cell count (>7.0×10^9 cells/L) p<0.04	n (%)	98 (52)	<0.01	129 (40)	NS	134 (45)	<0.01
High hematocrit (>43.5%) NS	n (%)	97 (51)	NS	160 (50)	NS	149 (50)	NS
High total cholesterol (>220 mg/dL) p<0.0001	n (%)	121 (64)	<0.01	159 (49)	<0.05	122 (41)	<0.01

ratio more than 0.8, from north to south there was a progressive decrease of cardiovascular events but this data was not significant probably because of the small number of patients included in this analysis.

Discussion

This study provides evidence that ,also in the setting of PVD, fibrinogen is influenced by several factors which have already been demonstrated to affect it in a healthy population or other clinical settings. Thus, fibrinogen was significantly associated with WBC count and serum cholesterol. Surprisingly, no significant association was observed with smoking, which is considered to strongly influence fibrinogen. However, this influence has been derived prevalently from studies performed in healthy populations, therefore it cannot be excluded that in patients with overt atherosclerosis smoking may play a minor role. However, in our study smoking habit was not confirmed by a verification test. It has been demonstrated that smoking's effect on fibrinogen is dose related[13] and that fibrinogen and carboxyhemoglobin levels are statistically correlated.[14] Further study, therefore, is necessary to explain our data.

We also sought to analyze whether the plasma levels of fibrinogen were related to the severity of atherosclerosis. The ankle/arm pressure ratio is an index which is quite sensitive indicator of the degree of peripheral vascular disease[15] and is predictor of cardiovascular complications.[8,16] Patients with an ankle/arm pressure ratio below 0.8, which identified those with more severe atherosclerosis,[17] did not show

Table 5. Regional distribution of cardiovascular events during the follow-up.

	North	*p value*	*Middle*	*p value*	*South*	*p value North vs. South*
All patients	(n=649)		(n=885)		(n=577)	
Cardiovascular events n (%) p<0.02	82 (13)	NS	116 (13)	<0.02	48 (8)	<0.02
Patients with previous surgery and ankle-arm index less than 0.8	(n=139)		(n=132)		(n=48)	
Cardiovascolar Events n (%) NS	26 (19)	NS	23 (17)	NS	6 (12)	NS

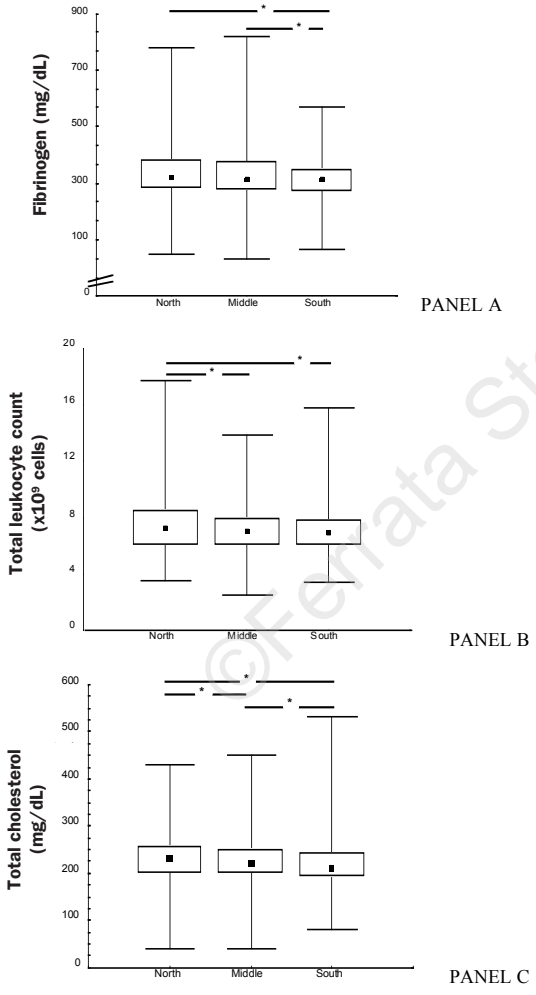

Figure 1. Fibrinogen plasma levels (Panel A), WBC count (Panel B) and total cholesterol serum levels in North (n=649), Middle (n=885) and South (n=577) of Italy. Symbols utilized in the Figures: *, p<0.01 (Mann-Whitney U test), ⊼ min max; ▭ CL: 25%-75%; ■ Median value

a higher prevalence of elevated plasma levels of fibrinogen suggesting that the severity of atherosclerosis does not affect fibrinogen values. The relationship between fibrinogen and degree of atherosclerosis has already been studied in other clinical settings such as coronary and cerebral vascular diseases but the results are conflicting since not all the studies reported that fibrinogen levels are related to the severity of atherosclerosis.[18-21] The use of more sensitive instrumental approaches to screen for the degree of vascular disease is needed to solve this issue.

The intriguing information of our study is that different areas of Italy are differently associated with fibrinogen levels. Thus in the south of Italy fibrinogen values were lower than in the middle and north. We could exclude at least 3 factors which might potentially bias this finding. The most important was the randomization period since it is known that fibrinogen has seasonal variations with higher values during the winter.[22] The randomization period of this study lasted 8 months with no significant difference of randomisation time among the 3 areas. The second potential bias was the method of measuring fibrinogen, which could vary among the centres involved in the study. However, 95% of centres used the Clauss method to measure fibrinogen. The third potential bias could result from *a posteriori* division of the country areas with an ensuing elimination of potential confounding factors. This possibility was excluded by the fact that we defined *ab initio* the areas which were to be considered as components of north, middle and south of Italy. Multiple logistic regression analysis confirmed that areas of Italy were independently associated with high plasma fibrinogen values so indicating that in the south of Italy there are some determinants which may contribute to lower fibrinogen levels. There are theoretically 3 determinants which may reduce fibrinogen in the south of Italy. One factor could be the temperature which is higher in this area of Italy and could affect the fibrinogen concentration as a consequence of a reduced rate of infections or chronic inflammation. Diet may be another important element, since, for instance, it is known that a

diet rich in ω-3 fatty acids reduces fibrinogen.[23] In the south of Italy the diet is particularly rich in fish, but it cannot be excluded that other dietary components may also play a role. Another possibility is that the variation of fibrinogen genotype which can be detected in PVD patients and is associated with higher fibrinogen values,[24] is less represented in the south of Italy. In this study we did not seek to analyze whether alcoholism might influence the regional distribution of fibrinogen. However, to our knowledge, there is no information available in our country suggesting that alcohol abuse is more prevalent in the north and middle Italy than the south of Italy. Since the initial hypothesis of the ADEP trial was not addressed to evaluate the concentration of fibrinogen in the 3 geographic parts of Italy, a potential limitation of our finding is that it results from a *post-hoc* analysis. However, the demonstration that more than one risk factor for atherosclerosis has a different geographic distribution could support the demonstration that fibrinogen concentration is lower in the south than in other areas of Italy.

Thus, WBC count and serum cholesterol levels were not uniformly distributed as shown by the fact that both were more frequently elevated in the north than middle and south of Italy. This data raises the question as to whether such non homogeneous prevalence of risk factors may account for different rates of cardiovascular diseases in PVD populations. In fact, two large trials which used the same inclusion criteria, demonstrated that claudicant patients have a large variability in terms of annual rate of cardiovascular events, which in fact ranged from 11 to 17%.[7,25] Our report may offer a possible explanation for this discrepancy, since we found that a PVD population has a non homogeneous distribution of risk factors with a lower prevalence of risk factors in the south of Italy. We do not have conclusive data to affirm that this finding accounts for a different cardiovascular risk, in part because the rate of events examined was low. However, it is noteworthy that the annual rate of cardiovascular events was lower in the south (12%) than the middle (17%) and north (19%) of Italy. Future trials in PVD subjects should, therefore, take these data into careful consideration, particularly in the case of interventional studies.

In conclusion, this study shows that in a population of patients with PVD, fibrinogen values are significantly associated with WBC count and serum cholesterol. Conversely, there is no significant association with the severity of PVD. The independent association between areas of Italy and fibrinogen also suggests that some not yet identified factors affect fibrinogen. Identification of these factors could be useful to plan strategy for reducing fibrinogen levels. Finally, our findings raise the question as to whether the large variability of cardiovascular events so far reported in PVD is related to a different distribution of risk factors.

Contributions and Acknowledgments

SB was responsible for randomization, data handling, statistical analysis and interpretation. MM was responsible for the conception of the study, its design, ethical approval. AL was responsible for randomisation, data handling and statistical analysis. MV contributed to the analysis and writing of the paper. LI contributed to the analysis and writing of the paper. FV was the principal investigator and formulated the design of the study, was the co-ordinator of the ADEP study. ADEP Group includes all the investigators in the 18 areas of Italy.

Disclosures

Conflict of interest: none.

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Manuscript processing

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