Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 45, No. 1, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2004.09.051

A Pharmacogenetic Effect of Factor XIII Valine 34 Leucine Polymorphism on Fibrinolytic Therapy for Acute Myocardial Infarction

Francisco Marín, MD, PHD,* Rocío González-Conejero, PHD,† Kaeng W. Lee, MRCP,‡ Javier Corral, PHD,† Vanessa Roldán, MD, PHD,§ Francisca López, MD,‖ Francisco Sogorb, MD,* Juan Caturla, MD, PHD,‖ Gregory Y. H. Lip, MD, FESC, FACC,‡ Vicente Vicente, MD, PHD†
Alicante and Murcia, Spain; and Birmingham, England

OBJECTIVES The aim of this study was to evaluate the pharmacogenetic role of the factor XIII (FXIII) valine 34 leucine (Val34Leu) polymorphism in the fibrinolytic therapy of acute myocardial infarction (MI).

BACKGROUND Fibrinolytic therapy is an established treatment for acute MI, but up to 40% of treated patients do not achieve optimal tissue reperfusion. The FXIII Val34Leu polymorphism is one of the most relevant functional polymorphisms described in the haemostatic system. The common Leu34 allele associates with an increased FXIII-transglutaminase activity, which results in an increased and faster rate of fibrin stabilization.

METHODS We genotyped this polymorphism in 293 consecutive MI patients (62 ± 12 years; 231 males) from two different European populations. All patients were treated with standard doses of fibrinolytic drugs. Noninvasive assessment of the efficacy of coronary fibrinolysis was evaluated by serial electrocardiograms and creatine kinase time-activity curves. The clinical outcome was also re-evaluated at 24 h (death, reinfarction, or urgent revascularization).

RESULTS Multivariate analysis showed that Leu34 carriers displayed a significantly less efficient fibrinolysis than carriers of Val/Val genotype ($p = 0.021$; odds ratio [OR] 1.90, 95% confidence interval [CI] 1.10 to 3.28). At 24 h, Leu34 allele carriers had the worst outcome ($p = 0.006$; OR 2.14, 95% CI 1.25 to 3.68). Interestingly, the combination of the Leu34 allele and nonsmoking status increased the risk of non-reperfusion criteria ($p = 0.003$, OR 3.77), and worse outcomes at 24 h ($p = 0.001$, OR 4.55).

CONCLUSIONS In a large cohort of nonselected and consecutive acute MI patients from two different European populations, we show clinical evidence that the presence of the Leu34 allele reduces the efficacy of fibrinolytic therapy. (J Am Coll Cardiol 2005;45:25–9) © 2005 by the American College of Cardiology Foundation

Fibrinolytic therapy is used to achieve the most important objective in patients with an acute myocardial infarction (MI), to open quickly the coronary flow after the occurrence of an acute coronary occlusion. Indeed, fibrinolytic therapy leads to better survival, recovery of left ventricular function, and remodelling following acute MI (1–3). Unfortunately, approximately 40% of treated patients do not achieve optimal tissue perfusion (4), and the potential benefits are limited by early (thrombotic) re-occlusion of the infarct-related artery (5). However, few factors have been identified to be involved in this inter-individual heterogeneity, such as age, delay between symptom onset and fibrinolytic therapy, smoking habit, and infarct size or site (6,7).

Coagulation factor XIII (FXIII) is a tetrameric structure consisting of two A (active) and two B subunits. Calcium and thrombin activate factor XIII in the final phase of the coagulation process. Activated FXIII catalyzes the formation of covalent gamma-glutamyl-gamma-lysine bonds between fibrin monomers, increasing the resistance of fibrin to degradation by plasmin (8). Multiple polymorphisms have been described in the FXIII-A subunit gene. A common G-to-T polymorphism in exon 2 causes a valine (Val) to leucine (Leu) change at position 34, three amino acids upstream to the thrombin cleavage site. This Val34Leu polymorphism affects the function of FXIII by increasing the rate of FXIII activation by thrombin, which results in an increased and faster rate of fibrin stabilization (9,10). However, the thrombotic role of this polymorphism is controversial and might be specific to populations (11–14).

In a small and retrospective cohort of survivors of premature MI, our group observed—for the first time—that Leu34 allele carriers could show more "resistance" to fibrinolytic therapy (15). In the present report, we prospectively studied an unselected, consecutive cohort of acute MI patients, eligible for fibrinolytic treatment, from two different European populations, and noninvasively assessed the efficacy of fibrinolytic therapy. Again, our hypothesis was that the presence of the Leu34 allele reduces the clinical efficacy of fibrinolytic therapy for acute MI.

From the *Cardiology Department, Hospital General Universitario, Alicante, Spain; †Centro de Hemodonación, Universidad de Murcia, Murcia, Spain; ‡Haemostasis, Thrombosis, and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, England; §Hematology Unit, Hospital de San Vicente, Alicante, Spain; and the ‖Intensive Care Unit, Hospital General Universitario, Alicante, Spain. This study has been supported by FIS 00/0328 and SAF2003-00840 (MCYT & FEDER). Drs. Corral and González-Conejero are Contratados de Investigación Ramón y Cajal from the Universidad of Murcia.

Manuscript received July 29, 2004; revised manuscript received September 9, 2004, accepted September 20, 2004.

Abbreviations and Acronyms

CI = confidence interval
CK = creatine kinase
FXIII = factor XIII
Leu = leucine
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
Val = valine

PATIENTS AND METHODS

Patients. From September 2002 to March 2004, we included 293 consecutive acute MI patients (mean age 61.8 ± 12.3 years; 231 males) from two different European populations: 170 from City Hospital, Birmingham, United Kingdom (this consisted of 109 white Caucasians and 61 Indo-Asians) and 123 from Hospital General Universitario, Alicante, Spain (all white Caucasian), who were eligible for fibrinolytic therapy. Both are University tertiary hospitals with 800 and 915 beds, respectively. Although at the time of this study there was no formal primary percutaneous coronary intervention (PCI) program for acute MI in both hospitals, about 88 patients were not included in the present study as primary PCIs were performed. All recruited subjects gave their informed consent to enter the study, which had been approved by the local research committee and was performed in accordance with the Declaration of Helsinki, as amended in Edinburgh in 2000.

Major cardiovascular risk factors (current smoking status, hypercholesterolemia, diabetes and hypertension) were recorded. Clinical features of patients and controls are indicated in Table 1. All patients were treated with standard doses of fibrinolytic drugs (tenecteplase, n = 199; streptokinase, n = 87; and recombinant tissue plasminogen activator, n = 9). Delay in initiation of fibrinolytic drugs from symptom onset was recorded.

Assessment of efficacy of fibrinolysis and outcome. Noninvasive assessment of the efficacy of coronary fibrinolysis was evaluated by a combination of clinical assessment, serial electrocardiograms and creatine kinase (CK) time-activity curves. A 12-lead electrocardiogram was registered at 0, 30, 60, 90, 120, 180, 240, and 300 min after fibrinolysis initiation. Blood samples for CK determination were drawn at 0, 3, 6, 9, 12, 15, and 21 h after fibrinolysis initiation. A resolution of ST-segment elevation more than 50% at 90 min and an early peak of CK (≤12 h) were considered as reperfusion criteria (16). All electrocardiograms were reviewed by two investigators who had no knowledge of the genetic determinations. When electrocardiograms were considered not interpretable (four patients) the early peak of CK was considered as the unique reperfusion criteria. The efficacy of fibrinolysis and the clinical outcome were also re-evaluated at 24 h (death, reinfarction, or necessity of urgent PCI).

Determination of FXIII Val34Leu genotype. Total genomic deoxyribonucleic acid was obtained from the white blood cell following the instruction of the Wizard genomic deoxyribonucleic acid purification system (Promega Innogenetics, Madrid, Spain). Genomic polymerase chain reaction of the FXIII-A chain exon 2 gene was performed with mutated primers, essentially as indicated elsewhere (17). The FXIII genotype was established after restriction of the polymerase chain reaction product with Bsa HI (17).

Statistical analysis. Results are expressed as mean value ± standard deviation for continuous variables and as percentages for categorical variables. Univariate statistical analysis was performed by the chi-square test. The strength of the association of the polymorphism with the occurrence of end points (reperfusion or clinical outcome at 24 h) was estimated by calculation of the odds ratio (OR) and the Cornfield method for the calculation of 95% confidence intervals (CIs). Multivariate analysis was performed using logistic regression, Enter method (adjusting by gender, age,

Table 1. Clinical Characteristic and Genetic Frequencies of Myocardial Infarction Patients

	All Patients	Mediterranean Caucasian	British Caucasian	British Indo-Asian
n	293	123	109	61
Age (yrs)	61.8 ± 12.3	61.5 ± 12.2	63.8 ± 11.0	59.0 ± 14.2
Male gender (%)	231 (78.8)	104 (84.6)	70 (73.4)	47 (77.0)
Smoking habit (%)	144 (49.1)	73 (59.3)	52 (47.7)	19 (31.1)
Hypertension (%)	140 (47.8)	60 (48.8)	52 (47.7)	28 (45.9)
Diabetes (%)	74 (25.3)	31 (25.2)	18 (16.5)	25 (41.0)
Hypercholesterolemia (%)	145 (49.5)	53 (43.1)	56 (51.4)	36 (59.0)
Genotype (%)				
Val/Val	184 (62.8)	80 (65.0)	61 (56.0)	43 (70.5)
Val/Leu	96 (32.8)	38 (30.9)	42 (38.5)	16 (26.2)
Leu/Leu	13 (4.4)	5 (4.1)	6 (5.5)	2 (3.3)
Allele				
Val34	0.792	0.805	0.752	0.836
Leu34	0.208	0.195	0.248	0.164

Hypertension was defined as blood pressure >140 mm Hg systolic or >90 mm Hg diastolic on repeated observations, or if no blood pressure values were available when the subject was under treatment with chronic antihypertensive therapy. Current/former smoker was considered when the subject smokes more than 10 cigarettes per day. Hypercholesterolemia was defined as a total serum cholesterol level >5.72 mmol/l (220 mg/dl).
Val = valine; Leu = leucine.

Table 2. Risk Factors for Non-Reperfusion Following Fibrinolytic Therapy for Acute Myocardial Infarction

	Crude OR (95% CI); p Value	Adjusted OR (95% CI); p Value
Age	1.00 (0.98–1.02); p = 0.914	0.98 (0.96–1.01); p = 0.240
Male gender	1.09 (0.60–1.99); p = 0.789	1.01 (0.52–1.98); p = 0.968
Smoker	0.72 (0.44–1.19); p = 0.210	0.63 (0.35–1.13); p = 0.120
Diabetes mellitus	1.38 (0.80–2.40); p = 0.251	1.31 (0.71–2.44); p = 0.386
Hypercholesterolemia	1.12 (0.69–1.83); p = 0.648	1.20 (0.70–2.06); p = 0.497
Hypertension	1.18 (0.72–1.92); p = 0.515	1.12 (0.63–1.97); p = 0.705
Fibrinolytic drug	0.92 (0.70–1.20); p = 0.523	0.83 (0.58–1.20); p = 0.326
Ethnicity	1.05 (0.88–1.26); p = 0.607	1.11 (0.87–1.41); p = 0.419
Time delay		
Q1–Q2	1.23 (0.60–2.53); p = 0.580	1.30 (0.61–2.79); p = 0.493
Q1–Q3	1.28 (0.63–2.60); p = 0.502	1.46 (0.69–3.07); p = 0.318
Q1–Q4	1.37 (0.67–2.83); p = 0.392	1.34 (0.62–2.87); p = 0.454
FXIII Leu34 allele carrier	1.65 (1.00–2.73); p = 0.049	1.90 (1.10–3.28); p = 0.021

Univariate analysis performed by chi-square test. Multivariate analysis performed by logistic regression, Enter method. Time delay analyzed by quartile intervals, all compared with Q1. Time delay: Q1: ≤90 min; Q2: 91–139 min; Q3: 140–240 min; Q4: >240 min.
CI = confidence interval; FXIII = factor XIII; Leu = leucine; OR = odds ratio; Q = quartile.

time delay, cardiovascular risk factors, ethnicity, and fibrinolytic agent). Statistical analysis was performed using the SPSS statistical package for Windows 10.0 software (SPSS Inc., Chicago, Illinois) and Epi-Info software (Centers for Disease Control and Prevention, Atlanta, Georgia). Differences with a two-tailed p value <0.05 were considered significant.

RESULTS

Clinical characteristics and genetic frequencies are summarized in Table 1. We did not detect any age or gender differences, and the distribution of genotypes was not significantly different from Hardy-Weinberg proportions (data not shown). The prevalence of the FXIII Val34Leu polymorphism in the different ethnic groups (Val/Leu + Leu/Leu: Mediterranean Caucasians 35.0%; British Caucasians 44.0%; and Indo-Asians 29.5%) was broadly similar to that previously described (11–14,17).

Fibrinolytic therapy. In the univariate analysis, only the FXIII Val34Leu polymorphism was statistically associated with the efficacy of fibrinolytic therapy (Table 2) and clinical outcome at 24 h (Table 3). The percentage of efficacy of fibrinolytic drugs was 60.6% in Leu34 allele carriers versus 71.7% in patients with the Val/Val genotype (p = 0.049; OR 1.65, 95% CI 1.00 to 2.73). Moreover, 52.3% of Leu34 allele carriers were free of end points at 24 h, compared to 65.8% of patients with the Val/Val genotype (p = 0.023; OR 1.75, 95% CI 1.08 to 2.84). There were no statistically significant differences in the success rate of fibrinolytic therapy between clinical characteristics, age, type of fibrinolytic drugs, blood pressure, or time delay (Tables 2 and 3). Importantly, ethnicity did not have a significant influence on fibrinolytic efficacy or the 24-h outcome (Tables 2 and 3).

In the multivariate analysis (logistic regression), fibrinolysis in Leu34 allele patients was significantly less efficient than that achieved among patients carrying the Val/Val genotype (p = 0.021, OR 1.90, 95% CI 1.10 to 3.28) (Table 2). Re-evaluation at 24 h revealed that the FXIII Val34Leu polymorphism was the only factor displaying a significant role (p = 0.006, OR 2.14, 95% CI 1.25 to 3.68) (Table 3).

Smoking habit did not significantly influence fibrinolytic therapy efficacy on a crude analysis (Table 3), but after

Table 3. Risk Factors for Death, Reinfarction, or Urgent PCI at 24 h

	Crude OR (95% CI); p Value	Adjusted OR (95% CI); p Value
Age	0.99 (0.96–1.01); p = 0.573	0.98 (0.96–1.00); p = 0.079
Male gender	1.15 (0.65–2.04); p = 0.626	1.11 (0.58–2.14); p = 0.753
Smoker	0.71 (0.44–1.13); p = 0.149	0.56 (0.32–1.00); p = 0.049
Diabetes mellitus	1.34 (0.79–2.29); p = 0.277	1.45 (0.79–2.67); p = 0.231
Hypercholesterolemia	1.32 (0.83–2.12); p = 0.242	1.33 (0.78–2.25); p = 0.293
Hypertension	1.00 (0.63–1.60); p = 0.990	0.97 (0.55–1.69); p = 0.908
Fibrinolytic drug	0.98 (0.76–1.27); p = 0.877	0.87 (0.61–1.25); p = 0.452
Ethnicity	1.09 (0.92–1.30); p = 0.321	1.16 (0.91–1.47); p = 0.221
Time delay		
Q1–Q2	1.00 (0.49–2.02); p = 1.000	1.07 (0.51–2.25); p = 0.860
Q1–Q3	1.24 (0.62–2.45); p = 0.544	1.44 (0.71–2.97); p = 0.318
Q1–Q4	1.63 (0.81–3.35); p = 0.171	1.60 (0.77–3.68); p = 0.208
FXIII Leu34 allele carrier	1.75 (1.08–2.84); p = 0.023	2.14 (1.25–3.68); p = 0.006

Univariate analysis performed by chi-square test. Multivariate analysis performed by logistic regression, Enter method. Time delay analyzed by quartile intervals, all compared with Q1. Time delay: Q1: ≤90 min; Q2: 91–139 min; Q3: 140–240 min; Q4 >240 min.
Abbreviations as in Table 2.

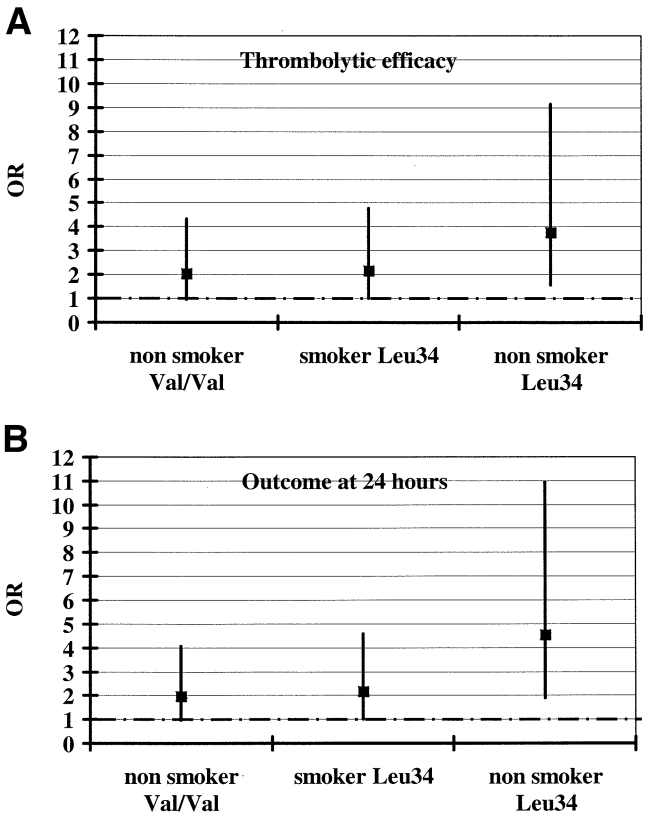

Figure 1. **(A)** Influence in fibrinolytic efficacy of the interaction between smoking habit and factor XIII Val34Leu polymorphism (logistic regression, Enter method, after adjusted by age, gender, cardiovascular risk factors, time delay, and fibrinolytic drug). **(B)** Influence in outcome at 24 h following fibrinolytic efficacy of the interaction between smoking habit and factor XIII Val34Leu polymorphism (logistic regression, Enter method, after adjusted by age, gender, cardiovascular risk factors, time delay, and fibrinolytic drug). Leu = leucine; OR = odds ratio; val = valine.

adjustment for clinical variables, this was associated with a better outcome at 24 h ($p = 0.049$).

As previous observations have described a higher rate of reperfusion in smokers (18–20), we also analyzed the possible synergistic interaction between FXIII Val34Leu polymorphism and smoking habit. In a multivariate analysis, the simultaneous combination of Leu34 allele and nonsmoking status increased the risk to non-reperfusion ($p = 0.003$, OR 3.77, 95% CI 1.55 to 9.16) and a worse outcome at 24 h ($p = 0.001$, OR 4.55, 95% CI 1.89 to 10.97) (Figs. 1A and 1B).

DISCUSSION

Consistent studies have demonstrated that primary PCI may be the preferred reperfusion strategy in acute MI, with reduction in death, reinfarction, and stroke compared to fibrinolytic therapy (21). Unfortunately, several features limit the availability of PCI in a significant proportion of patients (22). Hence, renewed interest has arisen about initiatives that could improve the fibrinolytic efficacy, including pre-hospital fibrinolysis programs, new therapeutic agents (tenecteplase), or new pharmacological reperfusion strategies (e.g., half-dose fibrinolytic agent plus glycoprotein IIb/IIIa receptor blockade) (23).

Pharmacogenetics has emerged as a new field in medicine that tries to identify gene variants able to explain the heterogeneity in patient response to a drug (24). Polymorphisms affecting disposition, metabolism, transporters, or targets of the drug could modify the individual response to one therapy, and its side effects (25). The present study explores the hypothesis that there is a genetic influence on fibrinolytic therapy efficacy, by analyzing the role of a common polymorphism that affects the target of fibrinolytic drugs. Only one recent study has analyzed the role of the C-1562T polymorphism affecting the promoter region of the matrix metalloproteinase-9 gene in the haemorrhagic transformation of stroke after fibrinolytic therapy in 61 patients, finding no significant effect (26). Therefore, to the best of our knowledge, our study is the first prospective one supporting a significant pharmacogenetic effect of one polymorphism in fibrinolytic therapy.

The main finding of the present prospective study in two different European populations (including three ethnic groups—Mediterranean white Caucasians, British white Caucasians, and British Indo-Asians) is that FXIII Val34Leu polymorphism was independently associated with less efficient fibrinolysis for acute MI. Accordingly, Leu34 allele carriers had a two-fold risk to not achieve optimal reperfusion, as well as a worse outcome at 24 h. These results are similar to those observed in a previous small and retrospective cohort of survivors of premature MI (15). All our results support the observation that the FXIII Val34Leu polymorphism could modify the therapeutic effect of fibrinolytic drugs, and this presumption is also supported by the biochemical and haemostatic effect of the FXIII Val34Leu polymorphism: the Leu34 allele associates with increased FXIII activation by thrombin, affecting the structure and resistance of the cross-linked fibrin clot (10).

Additionally, our study suggests a synergistic effect between FXIII Val34Leu polymorphisms and smoking. The simultaneous combination of one Leu34 allele and nonsmokers significantly increases the risk of poorer efficacy of fibrinolysis and a worse 24-h outcome. Smoking habit has been demonstrated to modify the effect of fibrinolytic therapy, with the highest reperfusion rate in smokers (18–20). Different hypotheses in this setting relate to a greater contribution of thrombus to the initiation of coronary occlusion (18) and impaired acute endogenous fibrinolytic capacity in smokers (27). Both mechanisms could enhance the influence of the FXIII polymorphism. These results support that a combination of genetic and environmental factors could explain the broad heterogeneity of fibrinolytic therapy efficacy.

Interestingly, the influence of the FXIII Leu34 allele on fibrinolytic therapy was similar in the three main populations analyzed in our study, even after adjusting for several possible confounders. This is relevant because the prothrombotic role of this polymorphism has been suggested to be different in the three populations (11–14,17).

Study limitations. One possible limitation of our study may be the assessment of the reperfusion efficacy by classical noninvasive criteria (16). To achieve optimal Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 has been considered the goal of reperfusion (6,28), with independent prognostic value (29). However, recent studies have demonstrated renewed interest in ST-segment recovery as an accurate marker of myocardial reperfusion (30,31), whereas time-activity curves of myocyte necrosis markers have been consistently described as good indices of reperfusion (31–33).

In conclusion, in a prospective cohort of nonselected consecutive acute MI patients from three different ethnic groups, we show clinical evidence that the FXIII Leu34 allele reduces the efficacy of fibrinolytic therapy and confers the worst clinical outcome at 24 h. Additionally, a synergistic association is observed between smoking habit and FXIII polymorphism. The present findings could have important influence in clinical practice. For example, the development of a rapid determination of FXIII Val34Leu polymorphism at bedside could help determine the more appropriate reperfusion strategy in acute MI patients, informing clinicians on the necessity of performing an urgent PCI or planning the possibility of rescue angioplasty.

Reprint requests and correspondence: Prof. Vicente Vicente, Centro Regional de Hemodonación, Ronda de Garay s/n 30003, Murcia, Spain. E-mail: Vicente.Vicente@carm.es.

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