Polymorphisms of the Interleukin-1β Gene Affect the Risk of Myocardial Infarction and Ischemic Stroke at Young Age and the Response of Mononuclear Cells to Stimulation In Vitro


**Objectives**—To investigate the role of interleukin-1β (IL-1β) gene polymorphisms as a link between inflammation, coagulation, and risk of ischemic vascular disease at young age.

**Methods and Results**—A total of 406 patients with myocardial infarction (MI) at young age, frequency-matched for age, sex, and recruitment center, with 419 healthy population-based controls and 134 patients with ischemic stroke at young age, matched by age and sex, with 134 healthy population-based controls, were studied. Subjects carrying the TT genotype of the −511C/T IL-1β polymorphism showed a decreased risk of MI (odds ratio [OR], 0.36; 95% CI, 0.20 to 0.64) and stroke (OR, 0.32; 95% CI, 0.13 to 0.81) after adjustment for conventional risk factors. In both studies, the T allele showed a codominant effect (P=0.0020 in MI; P=0.021 in stroke). Mononuclear cells from volunteers carrying the T allele showed a decreased release of IL-1β and a decreased expression of tissue factor after stimulation with lipopolysaccharide compared with CC homozygotes. The presence of a monoclonal antibody against IL-1β during cell stimulation resulted in a marked reduction of tissue factor activity expression.

**Conclusions**—−511C/T IL-1β gene polymorphism affects the risk of MI and ischemic stroke at young age and the response of mononuclear cells to inflammatory stimulation. (Arterioscler Thromb Vasc Biol. 2005;25:222-227.)

**Key Words:** risk factors ■ genetics ■ stroke ■ myocardial infarction ■ inflammation ■ coagulation

Increased levels of inflammatory markers are associated with ischemic vascular disease. Inflammation has a relevant role in the initiation and progression of atherosclerosis; however, it can also play a primary role in thrombosis development by activating the coagulation process. Interleukin-1β (IL-1β), a proinflammatory cytokine, stimulates the synthesis of tissue factor (TF) from monocytes and endothelial cells. TF triggers activation of the coagulation cascade toward thrombus formation. Inflammatory responses show a high interindividual variability and have been associated with polymorphisms in IL-1β gene; the latter have also been related to the risk of several chronic inflammatory diseases. We hypothesized that IL-1β gene polymorphisms might modulate the inflammation-triggered pathway of thrombus formation and the risk of ischemic arterial disease such as myocardial infarction (MI) and ischemic stroke. Patients with early-onset disease represent a subset of individuals in whom the impact of genes is more expressed and can be more easily identified.

Therefore, we investigated whether the risk of MI and ischemic stroke at young age is associated with polymorphisms in IL-1β gene and whether these polymorphisms can influence thrombosis by modulating the IL-1β–mediated TF activation in response to inflammation.

**Methods**

**Study Population**

**Patients With MI**

Between May 1995 and July 2002, 430 patients <45 (males) or <50 (females) years of age admitted to cardiology centers (see the list in the Appendix) with a first episode of MI were consecutively included into the study. Acute MI was defined as resting chest pain lasting >30 minutes accompanied by ST-segment elevation evolving into pathologic Q waves and was confirmed by total creatinine kinase or muscle brain fraction levels of more than twice the upper normal limit.

**Patients With Ischemic Stroke**

A total of 142 patients <45 years of age consecutively admitted to the Department of Neurology of Brescia University Teaching Hos-
pital with first-ever cerebral ischemia were also included. Stroke was defined as a sudden loss of global or focal cerebral function that persisted for >24 hours with a probable vascular cause. In all cases, suspected cerebral infarction was confirmed by brain CT or MRI. Briefly, the standard protocol included neurological examination, extracranial Doppler ultrasonography with frequency analysis and B-mode imaging, transcranial Doppler, 12-lead ECG, transthoracic or transeosophageal echocardiography, and standard blood tests. Magnetic resonance angiography or conventional angiography of the neck and cerebral vessels were performed in selected cases.16,17

Controls

Controls were recruited from the general population through the health assurance list in the area surrounding the recruiting medical centers using age (5-year categories)- and sex-stratified random sampling in each recruitment center. The random sampling of controls was timed to partially coincide with case enrollment for each center and was specific for each of the 2 studies. There was an overlap ranging between 60% and 95% of the catchment areas of cases for the different recruitment centers; moreover, these areas were all located in the same geographic region in which people shared a common environment and access to healthy resources. Data on clinical history were collected directly from subjects by the Rose Questionnaire.18 Ischemic coronary, cerebral, and peripheral diseases were excluded on the basis of clinical history. Cases and controls were all unrelated Italian whites with all grandparents born in Italy. The participation rate of cases and controls ranged from 90% to 98% and 68% to 85%, respectively, in the different centers. A structured questionnaire was administered by a trained interviewer:19 family history of MI (≥1 first-degree relative with MI <60 years of age), smoking habits (“former smokers” were formerly smokers who currently did not smoke), history of lipid disorders (hypercholesterolemia [≥200 mg/dL], hypertriglyceridemia [≥200 mg/dL]), low high-density lipoprotein cholesterol [≤35 mg/dL], or current treatment with lipid-lowering drugs), systemic hypertension (≥140/90 mm Hg or current treatment with antihypertensive medication), diabetes (fasting glucose level ≥140 mg/dL or current treatment with antidiabetic drugs), and drug use. Body mass index was calculated as weight divided by height squared (kilograms per meters squared). The study was approved by the ethical committees of the participating institutions. All study participants agreed to give blood samples for DNA analysis and biochemical measurements by written informed consent.

Laboratory Measurements and Techniques

Blood samples were obtained after ≥3 months from the last clinical instabilization or percutaneous or surgical procedure caring of the morning after 12 hours of fasting. IL-1β −511C/T, −31C/T and +3953C/T polymorphisms were studied as described previously.11–13 An internal quality control of DNA with known genotype for IL-1β, evaluated by direct sequencing, was used. Moreover, 5% of DNA samples were restated. A correspondence of 100% among the genotypes was obtained. Fibrinogen and C-reactive protein (CRP) were determined in a centralized laboratory by functional clotting time assay (DASIT) and by immunoturbidimetric method (Roche). All samples were tested in duplicate by operators blinded to sample identity. The interassay coefficient of variation was 4.3% and 2.3%, respectively, for fibrinogen and CRP.

Effect of IL-1β −511 Polymorphisms on IL-1β Release and TF Expression of Mononuclear Cells

For functional studies, 145 healthy volunteers (70 males and 75 females 35±5 years of age) were studied. No subject had received medication or experienced allergic disease or infections within a period of 2 weeks before blood sampling. All volunteers had a CRP level <1 mg/dL.

Monocyte Isolation and Stimulation With Lipopolysaccharide

Freshly drawn whole blood was processed as described.20 The final mononuclear cell preparation was incubated with lipopolysaccharide (LPS; 0.1 μg/mL) for 6 and 24 hours. Cells were sedimented and disrupted for TF evaluation while IL-1β was measured in the supernatant. Each experiment was performed in duplicate by operators blinded to sample identity. In additional experiments (n=3), cells were incubated with LPS (0.1 μg/mL) for 6 hours in the presence or absence of monoclonal antibodies (MoAbs) directed against IL-1β or IL-1α (R&D Systems). IL-1β levels were assessed by high-sensitivity ELISA (Amersham Pharmacia Biotech). Procoagulant activity was assessed by a 1-stage clotting assay.20

Statistical Analysis

Sample size was powered to detect an odds ratio (OR) of >2 or <0.05, for an expected allele frequency of 0.39,21 with a power of 80% and the level of type I error α=0.01 (Bonferroni correction for multiple comparisons). Continuous variables were compared using ANOVA or the Kruskall–Wallis test according to their observed distribution. χ 2 test (or Fisher exact test in the presence of small frequencies) was used to compare discrete parameters. Allele and genotypes frequencies were determined by genotype count and compared with the values predicted by the assumption of Hardy–Weinberg equilibrium (exact test of Hardy–Weinberg proportion for multiple alleles).22 The coefficient of gametic linkage disequilibrium was calculated by likelihood methods in the control sample.23 ORs, together with their 95% approximate CIs, were calculated using unconditional logistic regression analysis. Adjusted ORs were obtained in multivariate logistic regression analysis with adjustment for the frequency-matched variables and for covariates selected among the potential confounding variables, which were associated with MI with a P value <0.20 in univariate analysis.24 The “c-statistic,” or area under the receiver operator characteristic curve, was reported to evaluate the validity of multivariate models. To better assess the model of inheritance of the polymorphisms,23 the effect of each polymorphism was coded as: βXr, βXc, or IL-1β in a multiple logistic regression model adjusted for covariates, with Xc=0, 0, 1, and Xr=0, 1, for genotype CC, CT, and TT; using this coding scheme, the parameters βr and βc represent recessive and dominant effect of the allele T. If βr and βc were not statistically significant, a codominant model was tested coding the role of the polymorphism with the use of a single term βXc, with Xc=0, 1, 2. The interaction effect between variables was measured by the Synergy Index (SI).24 The variables fibrinogen and CRP were analyzed on a logarithmic scale to remove positive skewness. Data for continuous variables were expressed as mean±SD; a 2-tailed P value <0.05 was chosen as the level of significance. All computations were performed using the SAS statistical package (Version 8.2 for Windows; SAS Institute).

Results

Characteristics of the MI Patients and the Controls

Samples from 406 cases and 419 controls were finally available for the analysis. All patients had an unequivocal episode of MI; 26% had also undergone coronary artery bypass surgery and 16% percutaneous coronary angioplasty. Coronary angiography had been performed in 328 (81%) patients and showed an elevated prevalence of significant coronary atherosclerosis (defined as the presence of 1 or more >50% stenosis in at least 1 major coronary artery): 45% of patients had multivessel and 48% single-vessel disease, but 7% had an apparently normal coronary tree. All traditional coronary risk factors but the frequency-matched variables were significantly more frequent in patients than in controls (Table I, available online at http://atvb.ahajournals.org).

IL-1β −511C/T Promoter Polymorphism and Risk of MI at Young Age

The frequency of the T allele in control group was 0.36 (95% CI, 0.33 to 0.39), significantly higher than in patients with premature MI (0.30; 95% CI, 0.27 to 0.33; χ 2=7.54; P=0.006). The genotype distribution of the −511C/T pro-
moter (Table 1) was in Hardy–Weinberg equilibrium in cases and controls ($\chi^2=1.44, df=1, P=0.23$; and $\chi^2=0.46, df=1, P=0.50$, respectively) and was significantly different between cases and controls.

ORs decreased with the genotypes in the following order: CC (OR=1) > CT > TT. In univariate (P=0.009) and multivariate (P<0.0001) analysis (codominant analysis). Homozygosity for the T allele conferred a significant protection against MI in univariate analysis and in multivariate models (Table 1). Further adjustment for fibrinogen and CRP levels did not modify the association of IL-1β−511T allele with MI frequency (OR for heterozygotes, 0.93; 95% CI, 0.61 to 1.45; OR for homoygotes, 0.45; 95% CI, 0.24 to 0.87; c-statistic, 0.82). Single term for codominance was statistically significant (β = −0.40±0.13; P=0.0020), whereas terms for recessive or dominant effects of T allele were not.

No association was found between −511C/T IL-1β polymorphism and common MI risk factors. In addition, the association between the T allele and the risk of premature MI did not change when it was evaluated according to (1) different genotypes of the +3953C/T polymorphism (multivariate SI for interaction, 0.34; 95% CI, 0.37 to 1.90); and (2) presence/absence of common risk factors: SI for −511C/T and smoking, 0.83 (0.47 to 1.45); hypertension, 0.88 (0.23 to 3.41); and hyperlipidemia, 0.60 (0.26 to 1.38). There was no difference in allele or genotype frequency in MI patients according to the number of affected vessels (P=0.80).

The linkage disequilibrium between −511C/T and −31C/T polymorphisms of IL-1β gene was virtually complete (D' = 0.99; P<0.0001), with the combinations C-C and T-T present in 99.9% of the inferred haplotypes. Because all results for −511C/T polymorphism also apply to −31C/T polymorphisms, only the first will be further mentioned.

### IL-1β +3953C/T Polymorphism and the Risk of MI at Young Age

The IL-1β +3953C/T polymorphism was in negative linkage disequilibrium with the −511C/T polymorphism in cases (D' = −0.60; P<0.0001) and in controls (D' = −0.52; P<0.0001). The genotype distribution of the +3953C/T polymorphism was in Hardy–Weinberg equilibrium in cases ($\chi^2=1.26; df=1; P=0.26$) and in controls ($\chi^2=1.49; df=1; P=0.22$; Table 1) and was similar between cases and controls. The frequency of the rare T allele in controls was 0.21 (95% CI, 0.19 to 0.24) and 0.21 in patients (95% CI, 0.18 to 0.24; $\chi^2=0.02; df=1; P=0.88$). ORs for different +3953C/T genotypes were not statistically different from unit (Table 1).

### TABLE 1. Genotype Distribution in Patients and Controls and Risk of MI at Young Age for the −511C/T Promoter Polymorphism and the +3953C/T Polymorphism of the IL-1β Gene

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Cases n=406 (%)</th>
<th>Controls n=419 (%)</th>
<th>Univariate OR (95% CI)</th>
<th>Model 1*</th>
<th>Model 2**</th>
</tr>
</thead>
<tbody>
<tr>
<td>−511CC†‡</td>
<td>195 (48)</td>
<td>174 (41)</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>−511CT</td>
<td>180 (44)</td>
<td>187 (45)</td>
<td>0.86 (0.64–1.15)</td>
<td>0.90 (0.67–1.21)</td>
<td>0.83 (0.58–1.18)</td>
</tr>
<tr>
<td>−511TT</td>
<td>31 (8)</td>
<td>58 (14)</td>
<td>0.48 (0.30–0.77)</td>
<td>0.48 (0.20–0.78)</td>
<td>0.36 (0.20–0.64)</td>
</tr>
<tr>
<td>+3953CT‡†</td>
<td>244 (61)</td>
<td>258 (63)</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>+3953TT</td>
<td>140 (35)</td>
<td>130 (31)</td>
<td>1.14 (0.85–1.53)</td>
<td>1.11 (0.82–1.50)</td>
<td>1.25 (0.87–1.79)</td>
</tr>
</tbody>
</table>

*Genotype distribution of −511C/T polymorphism, $\chi^2=9.32; df=2; P=0.009$.
#Genotype distribution of +3953C/T polymorphism, $\chi^2=2.74; df=2; P=0.25$.
*Multivariate logistic-regression analysis adjusted for age, sex and centre of recruitment (frequency-matching variables); c-statistic, 0.62 for −511C/T.
**Multivariate logistic-regression analysis adjusted for age, sex, center of recruitment, body mass index, smoking status, family history of MI, history of hyperlipidemia, hypertension, or diabetes; c-statistic, 0.83 for −511 C/T.
†Reference group.

### TABLE 2. Genotype Distribution in Patients and Controls and Risk of Ischemic Stroke at Young Age for the −511C/T Promoter Polymorphism of the IL-1β Gene

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Cases n=134 (%)</th>
<th>Controls n=134 (%)</th>
<th>Univariate OR (95% CI)</th>
<th>Model 1*</th>
<th>Model 2**</th>
</tr>
</thead>
<tbody>
<tr>
<td>−511CC†‡</td>
<td>66 (49)</td>
<td>52 (39)</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>−511CT</td>
<td>59 (44)</td>
<td>61 (46)</td>
<td>0.76 (0.46–1.27)</td>
<td>0.76 (0.47–1.27)</td>
<td>0.75 (0.44–1.29)</td>
</tr>
<tr>
<td>−511TT</td>
<td>9 (7)</td>
<td>21 (16)</td>
<td>0.34 (0.14–0.80)</td>
<td>0.34 (0.14–0.81)</td>
<td>0.32 (0.13–0.81)</td>
</tr>
</tbody>
</table>

Percentage of each group are between brackets.
*Genotype distribution of −511C/T polymorphism, $\chi^2=6.50; df=2; P=0.039$.
*Multivariate logistic-regression analysis adjusted for age and sex (frequency-matching variables); c-statistic, 0.57.
**Multivariate logistic-regression analysis adjusted for age, sex, smoking status, history of hyperlipidemia, hypertension, or diabetes; c-statistic, 0.72.
†Reference group.
After inclusion of the −511C/T and +3953C/T polymorphisms in multivariate analysis, only term for codominance effect of the −511C/T polymorphism was statistically significant ($\beta = -0.39 \pm 0.13; P = 0.0028$).

### Characteristics of Stroke Patients and Controls

Samples from 134 cases and 134 controls were available for analysis. Clinical characteristics of the subjects included in the study are shown in Table II (available online at http://atvb.ahajournals.org). Smoking habits and history of hypertension and of hypercholesterolemia were significantly more frequent in patients than in controls.

### IL-1β −511C/T Promoter Polymorphism and the Risk of Ischemic Stroke at Young Age

The frequency of the rare allele T was 0.38 (95% CI, 0.33 to 0.44) in controls and 0.29 (95% CI, 0.23 to 0.34; $P = 0.017$) in patients with juvenile stroke. The genotype distribution (Table 2) was in Hardy–Weinberg equilibrium in controls and in cases ($\chi^2 = 0.19, df = 1, P = 0.66$; and $\chi^2 = 0.76, df = 1, P = 0.38$, respectively) and significantly differed between cases and controls ($\chi^2 = 6.5, df = 2; P = 0.039$). Compared with the CC genotype, the OR associated to the CT genotype decreased in univariate and multivariate analyses (Table 2). The OR associated to the CT genotype was 0.75 (95% CI, 0.44 to 1.29) and to the TT genotype was 0.32 (95% CI, 0.13 to 0.81) in multivariate logistic analysis (c-statistic for the multivariate model, 0.71). Term for codomance was statistically significant (coefficient in logistic regression, $\beta = -0.46 \pm 0.20; P = 0.021$).

The association between the T allele and the risk of premature stroke did not change when it was evaluated according to the presence/absence of common risk factors: SI for −511C/T and smoking, 0.17 (0.02 to 1.82); hypertension, 0.31 (0.01 to 27); and hyperlipidemia, 0.48 (0.02 to 10.8).

### Effect of IL-1β −511 Polymorphisms on IL-1β Release and TF Expression of Stimulated Mononuclear Cells

Of 145 subjects investigated, 54 (37.2%) were CC homozygotes, 69 (47.6%) heterozygotes, and 22 (15.2%) TT homozygotes. The frequency of the T allele of IL-1$\beta$ was 0.38 (95% CI, 0.33 to 0.42) in controls and 0.29 (95% CI, 0.23 to 0.34; $P = 0.017$) in patients with juvenile stroke. The genotype distribution (Table 2) was in Hardy–Weinberg equilibrium in controls and in cases ($\chi^2 = 0.19, df = 1, P = 0.66$; and $\chi^2 = 0.76, df = 1, P = 0.38$, respectively) and significantly differed between cases and controls ($\chi^2 = 6.5, df = 2; P = 0.039$). Compared with the CC genotype, the OR associated to the CT genotype decreased in univariate and multivariate analyses (Table 2). The OR associated to the CT genotype was 0.75 (95% CI, 0.44 to 1.29) and to the TT genotype was 0.32 (95% CI, 0.13 to 0.81) in multivariate logistic analysis (c-statistic for the multivariate model, 0.71). Term for codomance was statistically significant (coefficient in logistic regression, $\beta = -0.46 \pm 0.20; P = 0.021$).

The association between the T allele and the risk of premature stroke did not change when it was evaluated according to the presence/absence of common risk factors: SI for −511C/T and smoking, 0.17 (0.02 to 1.82); hypertension, 0.31 (0.01 to 27); and hyperlipidemia, 0.48 (0.02 to 10.8).

Incubation of mononuclear cells with a MoAb against IL-1$\beta$ during LPS stimulation resulted in a marked reduction of TF activity to 56.2±3.6% (mean±SE; n=3). In contrast, an MoAb against IL-1$\alpha$ was unable to inhibit TF expression.

### Discussion

The presence of the common −511C/T polymorphism in the promoter of IL-1$\beta$ gene showed a protective effect on MI at young age. Homozygosity for the T allele was associated with a 64% protection against MI. The T allele showed a codominant effect because the ORs decreased with the genotypes according to the number of T alleles, and a formal test for codomance gave significant results. To verify these findings, we genotyped the same polymorphism in a second population with cerebral infarcts as premature ischemic vascular event and found similar results. In particular, homozygosity for the T allele was associated with an ~2-fold decrease in stroke risk. Again, the effect of the T allele was independent from other risk factors for stroke and increased with the number of alleles in a codominant way. Inflammation seems to be a prominent mechanism in cardiovascular disease because systemic markers of inflammation have been consistently associated with the risk of ischemic vascular disease.1–5 However, it is still unclear whether inflammation is a causal mechanism in, or a secondary phenomenon induced by, the ischemic process and whether it influences the process of atherosclerosis or thrombus formation. The evidence for an association between IL-1$\beta$ genetics and the risk of MI and ischemic stroke suggests a primary pathogenetic role of inflammation in such diseases. Moreover, IL-1$\beta$ polymorphism seems to be implicated in thrombus formation rather than in atherosclerosis progression because it did not discriminate either patients with or without coronary disease nor with single or multivessel disease.26 Findings from the group of patients with ischemic stroke further support this hypothesis. The fact that only a small proportion of stroke victims have a presumed atherosclerotic infarct in our series, as in others,27 prompts us to...
speculate that the process linking the IL-1β –511TT genotype to stroke is probably not related to atherosclerosis.

The hypothesis of a pathogenic link between the IL-1β –511C/T genotype and thrombosis is strengthened by the results of our functional ex vivo analysis. IL-1β is a major link between inflammation and coagulation; indeed, it is able to stimulate the synthesis of TF from monocytes and endothelial cells.7,8 According to our clinical findings, blood mononuclear cells from carriers of the “protective” T allele were also “protected” to activate coagulation in response to an inflammatory stimulus. In these carriers, the release of IL-1β on LPS stimulation was significantly lower than that from mononuclear cells of carriers of the C allele. The same mononuclear cells expressed a significantly lower amount of TF procoagulant activity after LPS stimulation. The specific inhibition of TF expression by MoAbs against IL-1β confirms the relevance of endogenous IL-1β in stimulating the expression of TF on cell surface. Thus, the –511C/T polymorphism could contribute to the risk of MI or ischemic stroke by modulating the cellular response to inflammatory stimuli and the subsequent promotion of blood clotting. Although LPS stimulation may represent an extreme model of inflammatory stimuli, the relevance of this test in vivo conditions has been largely described.9 Carriership of the T allele might confer a decreased susceptibility to MI and ischemic stroke through a decreased inflammatory response and a consequent decreased activation of blood coagulation.

The selection of population-based controls, the use of innovative statistical analysis for genetic models of inheritance, and the support of the ex vivo cellular response to inflammatory stimulation and subsequent development of prothrombotic activity strengthen the potential clinical meaning of these results. However, some limitations of this study should be considered. The polymorphisms studied do not extensively cover the IL-1β gene; therefore, the possibility that other functional variants might show association with MI in young patients cannot be excluded. We selected a number of polymorphisms compatible with the power of the study and took into account multiple comparisons on the basis of standard criteria,28 such as allele frequency, position in the gene, and demonstration of relevance, for inflammatory disease in other studies.10,12,29

Because of the young age of our study population, these findings can apply to young individuals and may not be generalized to other age groups. However, given the relevance of inflammatory mechanisms in the pathogenesis of ischemic disease at young age and the absence of association between the IL-1β –511C/T polymorphism and MI or stroke in older populations,30,31 the possibility of an age-dependent effect on the relationship of this genetic variant with ischemic disease cannot be excluded.

Finally, the number of diabetic patients included in our study might have been underestimated because they were diagnosed by “old” criteria such as those in current use when the protocol was prepared. However, this potential limitation should not have affected our results because the inclusion of diabetes in multivariate analysis did not modify the observed association of the polymorphisms with either MI or stroke risk; moreover, we failed to find any interaction between diabetes and IL-1β polymorphisms in modulating either MI or stroke risk.

In conclusion, our data support a primary role of inflammation-activated coagulation in the development of MI and ischemic stroke at young age and give the first evidence that the association between IL-1β and ischemic disease at young age is genetically modulated.

Appendix

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References
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on behalf of IGIGI Investigators

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Table I. Characteristics of the Patients with MI at young age and of their Controls

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<thead>
<tr>
<th>Characteristic</th>
<th>Cases N=406</th>
<th>Controls N=419</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Age – yr</td>
<td>41±5</td>
<td>40±5</td>
<td>0.13</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>346 (85)</td>
<td>356 (85)</td>
<td>0.92</td>
</tr>
<tr>
<td>Females</td>
<td>60 (15)</td>
<td>63 (15)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>258 (68)</td>
<td>152 (38)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Former smoker</td>
<td>66 (18)</td>
<td>48 (12)</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>54 (14)</td>
<td>195 (50)</td>
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<tr>
<td>History of Lipid disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Yes</td>
<td>217 (43)</td>
<td>90 (21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No</td>
<td>165 (57)</td>
<td>312 (79)</td>
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</tr>
<tr>
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<td>125 (34)</td>
<td>44 (11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No</td>
<td>243 (66)</td>
<td>340 (89)</td>
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<tr>
<td>History of Diabetes</td>
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<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>23 (6)</td>
<td>3 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No</td>
<td>351 (94)</td>
<td>383 (99)</td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>110 (35)</td>
<td>56 (18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No</td>
<td>203 (65)</td>
<td>256 (82)</td>
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</tr>
<tr>
<td>Body Mass Index – kg/m²</td>
<td>27±4</td>
<td>25±4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrinogen – mg/dl</td>
<td>268±68</td>
<td>245±63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C-Reactive Protein – mg/dl</td>
<td>0.20±0.28</td>
<td>0.19±0.44</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Plus-minus values are means ±SD. Percentage of each group are between brackets. For some variables, the sum of the strata does not necessarily add to the total because of missing values.
### Table II. Characteristics of the Patients with Stroke at young age and of their Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases N=134</th>
<th>Controls N=134</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr</td>
<td>35±7</td>
<td>35±8</td>
<td>0.71</td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
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</tr>
<tr>
<td>Males</td>
<td>69 (51)</td>
<td>69 (51)</td>
<td>0.99</td>
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<tr>
<td>Females</td>
<td>65 (49)</td>
<td>65 (49)</td>
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<tr>
<td>Smoking status</td>
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</tr>
<tr>
<td>Current smoker</td>
<td>59 (44)</td>
<td>54 (40)</td>
<td>0.0015</td>
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<tr>
<td>Former smoker</td>
<td>22 (16)</td>
<td>6 (5)</td>
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</tr>
<tr>
<td>Never smoked</td>
<td>53 (40)</td>
<td>74 (55)</td>
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<td>Yes</td>
<td>39 (29)</td>
<td>18 (13)</td>
<td>0.0017</td>
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<tr>
<td>No</td>
<td>95 (71)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (16)</td>
<td>10 (7)</td>
<td>0.036</td>
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<td>No</td>
<td>113 (84)</td>
<td>124 (93)</td>
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<td>4 (3)</td>
<td>0 (0)</td>
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<td>134 (100)</td>
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<tr>
<td>Yes</td>
<td>25 (20)</td>
<td>28 (15)</td>
<td>0.76</td>
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<tr>
<td>No</td>
<td>127 (80)</td>
<td>114 (85)</td>
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</tr>
<tr>
<td>Body Mass Index – kg/m²</td>
<td>24±4</td>
<td>24±5</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Plus-minus values are means ±SD. Percentage of each group are between brackets. For some variables, the sum of the strata does not necessarily add to the total because of missing values.