The Association of Hereditary Prothrombotic Risk Factors with ST-Elevation Myocardial Infarction

Kalıtsal Protrombotik Risk Faktörlerinin ST Yükselmeli Miyokart Enfarktüsü ile İlişkisi

İbrahim Halil Damar, Recep Eroz

ABSTRACT

Objective: The ST-elevation myocardial infarction (STEMI), a serious health care problem, is commonly a thrombotic complication of coronary artery disease. We compare the STEMI patients and control group in terms of the possible causes of inherited thrombophilia including FactorV Cambridge G1091C, FactorV Leiden G1691A, MTHFR C677T, MTHFR A1298C, FactorII G20210A, Factor XIII (V34L), ITGB3, ACE gene variants.

Methods: Fifty-three patients with STEMI and 47 individuals without diagnosis of acute coronary syndrome were included in the study. Percutaneous coronary intervention was performed for patients with STEMI. Echocardiography was performed and inherited thrombophilia genes were evaluated in all subjects.

Results: The MTHFR A1298C, Factor XIII (V34L), ITGB, ACE and homozigot or compound heterozigot gene variations of inherited thrombophilia are significantly related with STEMI (p<0.05). Also significantly higher MTHFR A1298C, FactorV Leiden G1691A, PAI and ACE gene variations in MI patients who were smokers; FactorV (V34L), PAI and ACE gene variations in MI patients with HT; PAI and ACE gene variation in MI patients with FH and PAI gene variations in MI patients with HL were detected when compared with the control groups with all of the same risk factors (p<0.05).

Conclusion: Hereditary thrombophilia factors may show promise in the prevention and management of STEMI when supported studies with larger case series.

Keywords: Coronary artery disease, inherited thrombophilia, STEMI, thrombosis, hypercoagulation

ÖZ

Amaç: Ciddi bir sağlık sorunu olan ST yükselmeli miyokart enfarktüsü (STEMI), genellikle koroner arter hastalığının thrombotik bir komplikasyonudur. STEMI hastalarını ve kontrol grubunu, FactorV Cambridge G1091C, FactorV Leiden G1691A, MTHFR C677T, MTHFR A1298C, FactorII G20210A, FaktörXIII (V34L), ITGB, ACE ve homozigot veya bileşik heterozigot veya bireysel heterozigot gen varlığına STEMI ile ilgili olarak ilişkilidiridir (p<0.05). Ayrıca sigara içen MI hastalarında MTHFR A1298C, FactorV Leiden G1691A, PAI ve ACE gen varlığını, HT'li MI hastalarında Faktör XIII (V34L), PAI ve ACE gen varlığını, aile öyküsü olan MI hastalarında PAI ve ACE gen varlığını ve HL’li MI hastalarında PAI gen varlığını anıtladığı derecede kontrol grubundan daha yüksek bulundu.

Sonuç: Kalıtsal trombofili faktörleri, daha büyük seriler çalışmalara desteklenmede STEMI nin önlenmesi ve tedavisi için unutulmamalıdır.

Anahtar kelimeler: Koroner arter hastalığı, kalıtsal trombofiliti, STEMI, tromboz, hiperkoagülasyon
INTRODUCTION

According to the World Health Organization data, around 17.9 million people died from cardiovascular diseases worldwide in 2016 which corresponds to 31% of all deaths in the world. Acute myocardial infarction and stroke were responsible for 85% of these deaths¹.

ST-elevation myocardial infarction (STEMI) is a condition in which acute myocardial ischemia develops due to the development of thrombosis, usually on background of coronary artery disease. Despite advanced methods of diagnosis and treatment, since the pathophysiology of the disease cannot be clearly revealed, STEMI is still a disease with high mortality and morbidity rates worldwide. At autopsy, atherosclerotic plaques of patients who died from STEMI primarily consist of a variable degree of fibrous tissue cells and overlapping thrombus. Coronary arterial thrombus is responsible for STEMI in most cases. Thrombus consists of platelets, fibrin, erythrocytes and leukocytes, and adheres to the luminal surface of the artery².

Although the presence of diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), smoking and obesity are blamed for the development of the disease, it is known that some genetic risk factors have very important effects too. There are genes related with possible causes of inherited thrombophilia [Factor V Cambridge G1091C, Factor V Leiden G1691A, MTHFR C677T, MTHFR A1298C, Factor II G20210A, Factor XIII (V34L), Plasminogen Activator Inhibitor-1 (PAI-1), FGB, ITGB3, APOB, FVHR2 and angiotensin-converting enzyme (ACE)]³.

To the best of our knowledge there was no study performed using broad range of the inherited thrombophilia factors including Factor V Cambridge G1091C, Factor V Leiden G1691A, MTHFR C677T, MTHFR A1298C, Factor II G20210A, Factor XIII (V34L), PAI-1, FGB, ITGB3, APOB, FVHR2, ACE genes in STEMI patients. Some of these genetic risk factors directly affect the formation of fibrin clots in the coagulation pathway. A demonstrative example of the mechanism of thrombus formation on the background of atherosclerosis is given under the guidance of coagulation pathway in Figure 1.

Therefore, we aimed to investigate frequencies of several inherited thrombophilia factors which may be potentially related with the coronary thrombosis and their association with clinical risk factors in patients with STEMI.

---

Figure 1. The mechanism of thrombosis formation on the background of atherosclerosis under the guidance of coagulation pathway.
MATERIAL and METHODS

Study design
In this study, thrombotic occlusion was evaluated by angiography in 53 patients who underwent percutaneous coronary intervention (PCI) for STEMI. Forty-seven patients without any history of acute coronary syndrome (ACS) and clinical findings suggestive of coronary artery disease were included in the control group. The diagnosis of acute myocardial infarction (AMI) was made according to the Fourth Universal Definition of Myocardial Infarction by considering clinical, electrocardiography (ECG), and cardiac enzyme findings. PCI was applied to the culprit lesion in patients undergoing coronary angiography. The lesion causing more than 50% reduction in lumen diameter in other coronary arteries was accepted as coronary artery stenosis and the lesion causing less than 50% narrowing was accepted as normal or near normal coronary arteries (N/NNCAs), which was not hemodynamically significant.

Hypercholesterolemia was defined as serum total cholesterol: ≥5.2 mmol/L, low density lipoprotein: ≥2.6 mmol/L, triglyceride: ≥1.7 mmol/L or use of cholesterol lowering drugs. Diabetes mellitus was defined based on fasting plasma glucose: ≥6.94 mmol/L (>125 mg/dL) levels or the use of antidiabetic therapy. Hypertension was defined as blood pressure ≥140/90 mmHg or antihypertensive drug use. Smokers were described as people who reported current smoking. Demographic features of the participants, laboratory findings (creatinine, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride, fasting blood glucose, white blood cells, hemoglobin level, platelet count, and C-reactive protein) were recorded. The study protocol was certified by the local Ethics Committee. Written informed consent was obtained from all participants. Patients with atrial fibrillation, moderate-to-severe valvular heart disease, congenital heart disease, uncontrolled hypertension, hypothyroidism, hyperthyroidism, malignancy, hepatic, renal, pulmonary and hematological disorders were excluded from the study. Total DNA was isolated using Magnesia 16 Complete Blood Genomic DNA Isolation Kit-102 in 200 ml peripheral blood samples obtained from the patients. Then Factor V Cambridge G1091C, Factor V Leiden G1691A, MTHFR C677T, MTHFR A1298C, Factor II G20210A, Factor XIII (V34L), PAI-1, FGB, ITGB3, APOB, FVHR2, ACE gene variants were evaluated in both STEMI and the control groups.

Electrocardiography
A resting 12-lead ECG (filter range, 0.05-150 Hz; AC filter, 60 Hz, 25 mm/s, 10 mm/mv) was recorded by available machine (NIHON KOHDEN Cardiofax ECG 1250K model) in all patients.

Echocardiography
Echocardiography was performed in all subjects included in the study using Siemens Acuson SC 2000 device. It was performed after PCI in patients with STEMI. Cardiac anatomy, valve functions, ejection fraction, and segmental wall motion abnormality were assessed using standardized projections and routine measurements were done according to the recommendations of the American Society of Echocardiography.

Coronary Angiography
All patients in the STEMI group included in the study underwent selective right and left coronary angiography and PCI using the standard Judkin’s technique with General Electric INNOVA 2100 IQ model device. Coronary arteries were visualized in the right and left oblique positions using cranial and caudal angulation. Images were digitally recorded at 15 frames per second.

Statistical analysis
Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, New York, USA). Normally distributed quantitative variables were expressed as mean±standard deviation and as median (minimum-maximum) in case of non-normal distribution. Quantitative variables were expressed as...
numbers and percentages. Differences between independent groups were assessed by Student t-test for normally distributed quantitative variables and Mann-Whitney U-test for variables without normal distribution and chi-square test for qualitative variables. Spearman’s correlation analyses were used to assess the correlations between thrombophilia parameters and cardiovascular risk factors. All results were considered statistically significant at the level of p<0.05.

RESULTS

Among demographic and laboratory findings, male sex frequency (44 (83%) vs. 26 (55.3%)), body mass index (27.9±4.5 kg/m² (19.4 kg/m² -40.2 kg/m²) vs. 25.3±4.0 kg/m² (17.6 kg/m² -36.0 kg/m²), heart rate (71.3±13.3 (51-108) bpm vs. 74.9±8.7 (49-86) bpm), diastolic blood pressure (86.0±8.6 (70-100) mmHg vs. 82.0±8.7 (60-100) mmHg), fasting blood glucose (105.1±17.1 (82-140) mg/dL vs. 90.4±9.2 (78-119) mg/dL), creatinine (0.83±0.17 (0.45-1.28) mg/dL vs. 0.73±0.19 (0.26-1.15) mg/dL), total cholesterol (172.4±48.0 (94-344) mg/dL vs. 185.6±34.1 (117-270) mg/dL), low-density lipoprotein (101.0±36.1 (40-185) mg/dL vs. 114.3±26.6 (56-167) mg/dL), white blood cell count (8417±2219 (17000-17000) vs. 6876±1873 (4000-11200)) and, C-reactive protein (0.5±0.3 (0.10-1.32) mg/dL vs. 0.4±0.2 (0.10-1.07) mg/dL) were significantly higher in STEMI patients than control group (Table 1). Among the echocardiographic findings, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), septum and posterior wall thicknesses were higher and left ventricular ejection fraction (EF) was lower in STEMI patients (Table 1).

| Age (years) | STEMI | Mean±SD (min-max) | Control | Mean±SD (min-max) | Z   | p  |
|-------------|-------|-------------------|---------|-------------------|-----|----|
| 57.98±8.111 (35-74) | 54.95±8.655 (40-71) | -1.870 | 0.061 |
| Sex | M:44 (83%)/F:9 (17%) | M:26 (55.3%)/F:21 (44.7%) | - | 0.03* |
| BMI (kg/m²) | 27.89±4.457 (19.38-40.15) | 25.27±3.986 (17.58-35.94) | -3.129 | 0.002* |
| HR | 71.30±13.311 (51-108) | 74.93±8.736 (49-86) | -2.217 | 0.027* |
| SBP (mmHg) | 133.77±20.496 (90-180) | 127.23±15.245 (100-160) | -1.475 | 0.140 |
| DBP (mmHg) | 86.03±8.625 (70-100) | 82.02±8.764 (60-100) | -1.940 | 0.052* |
| FBG (mg/dL) | 105.11±17.116 (82-140) | 90.36±9.242 (78-119) | -4.580 | 0.000* |
| Creatinin (mg/dL) | 0.83±0.174 (0.45-1.28) | 0.72±0.192 (0.26-1.15) | -2.722 | 0.006* |
| TC (mg/dL) | 172.35±48.021 (94-344) | 185.95±34.087 (117-270) | -1.931 | 0.054* |
| HDL (mg/dL) | 40.56±8.402 (29-67) | 46.89±12.541 (23-89) | -2.907 | 0.004* |
| LDL (mg/dL) | 100.98±36.136 (40-185) | 114.30±26.557 (56-167) | -2.280 | 0.023* |
| Triglyceride (mg/dL) | 151.69±93.039 (38-597) | 121.93±54.036 (37-269) | -1.578 | 0.115 |
| WBC | 8416.98±2219.038 (4700-17000) | 6876.59±1827.944 (4000-11200) | -3.613 | 0.000* |
| Hemoglobin (g/dL) | 14.14±1.473 (10.60-16.60) | 13.87±1.765 (9.90-16.50) | -0.667 | 0.505 |
| Platelets | 257.98±62.820 (166-475) | 279.44±73.967 (175-533) | -1.568 | 0.117 |
| CRP | 0.49±0.301 (0.10-1.32) | 0.35±0.244 (0.10-1.07) | -2.880 | 0.004* |

Echocardiographical Findings

| LVEDD (cm) | STEMI | 4.825±0.449 (4.5-9.00) | Control | 4.58±0.364 (3.60-5.30) | -2.354 | 0.019* |
| LVEDD (cm) | 3.60±0.466 (2.80-4.80) | 3.27±0.368 (2.30-4.10) | -3.716 | 0.000* |
| Septum (cm) | 1.16±0.194 (0.80-1.50) | 0.98±0.156 (0.7-1.5) | -4.679 | 0.000* |
| Posterior (cm) | 0.95±0.151 (0.50-1.20) | 0.87±0.107 (0.70-1.20) | -3.199 | 0.001* |
| EF (n %) | 54.24±9.477 (30-65) | 63.89±2.539 (55-65) | -6.863 | 0.000* |

BMI: Body mass index, SBP: Systolic Blood pressure, DBP: Diastolic Blood pressure (mmHg), FBG: Fasting Blood Glucose, TC: Total Cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, WBC: White Blood Cells, CRP: C-reactive protein, Min-Max: Minimum-Maximum, SD: Standard deviation, HR: Heart Rate, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, EF: Ejection Fraction
When two groups are compared in terms of cardiovascular major risk factors, the frequencies of diabetes mellitus (41.5% vs. 4.3%), hypertension (69.8% vs. 36.2%), hyperlipidemia (66% vs. 29.8%) and problematic family history (60.4% vs. 25.5%) were higher in STEMI group, while the frequency of smoking (43.4% vs. 46.8%) was similar in both groups (Table 2). When the groups were evaluated in terms of hereditary thrombophilia compared to the control group, significantly higher frequencies were detected in favor of STEMI; MTHFR A1298C (45.3% vs. 27.7%; p=0.008), FactorXIII (22.6% vs. 4.3%; p=0.008), ITGB (17% vs. 2.1%; p=0.013), ACE (del/del:37.7% and ins/del:37.7% vs. del/del:27.7% and ins/del:19.1%; p=0.0110) and homozygous or compound heterozygous gene variations as the possible causes of inherited thrombophilia ($X^2$=26.053; p<0.001) (Table 3).

When the distribution of inherited thrombophilia risk factors according to degree of vessel diseases was considered, statistically significant differences were detected for MTHFR A1298C ($X^2$=11.032; p=0.026) and Factor V Cambridge G1091C ($X^2$=6.698; p=0.035). Additionally, hereditary thrombophilic factors were significantly higher in MI patients with cardiovascular major risk factors than the control patients with the same cardiovascular major risk factors (Table 4).

### DISCUSSION

According to our results, a statistically significant difference between STEMI and control groups was detected for MTHFR A1298C, FactorXIII, ITGB, ACE and homozygous or compound heterozygous gene variations as the possible causes of inherited thrombophilia. Additionally, when the

---

**Table 2. Cardiovascular major risk factors of patients.**

|               | STEMI (n; %) | Control (n; %) | $X^2$ | p     |
|---------------|-------------|----------------|-------|-------|
| Diabetes mellitus | 22 (41.5%)  | 2 (4.3%)       | 18.954| 0.000*|
| Hypertension   | 37 (69.8%)  | 17 (36.2%)     | 11.349| 0.001*|
| Hyperlipidemia | 35 (66%)    | 14 (29.8%)     | 13.099| 0.000*|
| Cigarette using| 23 (43.4%)  | 22 (46.8%)     | 0.117 | 0.732 |
| FHCD           | 32 (60.4%)  | 12 (25.5%)     | 12.275| 0.000*|

*FHCD: Family History of Cardiovascular Disease*

**Table 3. Distribution of inherited thrombophilia factors in control and STEMI group.**

| Genes                  | Control (n, %) | STEMI (n, %) | $X^2$ | p     |
|------------------------|----------------|--------------|-------|-------|
| MTHFR A1298C           | Het:13 (27.7%) | Het:24 (45.3%) | 9.669 | 0.008*|
| Factor II G20210A      | Het:1 (2.1%)   | Het:3 (5.7%)  | 0.810 | 0.368 |
| Factor V Leiden G1691A | Het:1 (2.1%)   | Het:5 (9.4%)  | 3.416 | 0.181 |
| Factor V Cambridge G1091C | Het:0 (0%)     | Het:0 (0%)    | 0.896 | 0.344 |
| MTHFR C677T            | Het:18 (38.3%) | Het:19 (35.8%) | 0.564 | 0.754 |
| FactorXIII (V34L)      | Het:4 (4.3%)   | Het:12 (22.6%) | 6.994 | 0.008*|
| ITGB                   | -              | -             | -     | -     |
| FGB                    | -              | -             | -     | -     |
| APOB                   | -              | -             | -     | -     |
| FVHR2                  | 4G/5G:15 (31.9%) | 4G/5G:17 (32.1%) | 14.643 | 0.001*|
| PAI                    | 4G/4G:5 (10.6%) | 4G/4G:22 (41.5%) | -     | -     |
| ACE                    | del/del:13 (27.7%) | del/del:20 (37.7%) | 9.120 | 0.010*|
| Hom or Compound Heterozygous | 23 (48.9%) | 50 (94.3%) | 26.053 | 0.000*|

*Statistically significant, MTHFR: Methylenetetrahydrofolate reductase, ITGB: Integrin beta-1, FGB: β-fibrinogen gene, APOB: Apolipoprotein B, FVHR2: Factor V HR2, PAI: Plasminogen Activator Inhibitor-1, ACEI: Angiotensin Converting Enzyme Inhibitors
The effects of variation in some genes on thrombosis were evaluated but their association with thrombosis is controversial. The \textit{PAI (4G/5G polymorphism)}\(^9\) and \textit{ACE} (the D allele from the I/D polymorphism)\(^9\) have been shown as independent risk factors for MI. \textit{MTHFR C677T} polymorphism was shown not to be associated with STEMI\(^10\). \textit{ACE}, a key enzyme in the renin-on the regulation angiotensin system, has a crucial function in blood pressure control and the development of STEMI\(^9\). High angiotensin II levels and low bradykinin levels may cause a chronic state of increased vascular resistance and high blood pressure.

**Table 4. Relation between inherited thrombophilia and cardiovascular risk factors.**

| Genes | G | HT (n, %) | \(X^2/p\) | FH (n, %) | \(X^2/p\) | Smoking (n, %) | \(X^2/p\) | HL (n, %) | \(X^2/p\) |
|-------|---|----------|---------|---------|---------|--------------|---------|---------|---------|
| \textit{MTHFR A1298C} | C | - | - | NSA | - | Het:12 (52.2) | - | 5.678 | - |
| Factor Leiden | C | - | - | NSA | - | Het:5 (22.7) | 0.05* | - | - |

| Factor Pi (V) | p | 4.962 | - | - | - | Het:9 (24.3) | - | - | - |
| Hom: 0 (0) | NV:28 (75.7) | / | NSA | - | - | Het:4 (17.4) | - | 4.192 | - |
| Hom: 0 (0) | NV:19 (82.6) | / | NSA | - | - | Het:0 (0) | 0.040* | - | - |
| Hom: 0 (0) | NV:22 (100) | / | NSA | - | - | Het:0 (0) | 0.040* | - | - |

| PAI | 5G/5G:8 (21.6) | 8.813 | 12.5 | 5G/SG:6 (26.1) | 13.342 | 5G/SG:7 (20) | 5G/SG:13 (37.1) | 7.140 | 5G/SG:15 (50) |
| 4G/SG:13 (35.1) | / | (34.4) | 4G/SG:13 (13) | 4G/SG:14 (60.9) | 4G/SG:15 (42.9) | / | NSA | |
| 4G/SG:16 (43.2) | / | (34.4) | 4G/SG:13 (13) | 4G/SG:14 (60.9) | 4G/SG:15 (42.9) | / | NSA | |

| ACE | del/del:15 (40.5) | 7.303 | 21.7 | del/del:5 (21.7) | 7.715 | del/del:5 (21.7) | del/del:7 (31.8) | - | - |
| ins/del:14 (37.8) | / | (46.9) | ins/del:12 (52.2) | ins/del:6 (26.1) | / | ins/del:6 (26.1) | / | NSA | |
| ins/ins:8 (21.6) | / | (34.4) | ins/del:11 (52.2) | ins/del:6 (26.1) | / | ins/del:6 (26.1) | / | NSA | |
| ins/ins:10 (58.8) | / | (34.4) | ins/del:11 (52.2) | ins/del:6 (26.1) | / | ins/del:6 (26.1) | / | NSA | |

| Hom CH | p | 29.368 | 15.403 | 19.112 | 20.417 | 29.368 | 15.403 | 19.112 | 20.417 |
| CH | 1.2% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |
| Hom CH | 17.6% | 10.3% | 15.4% | 19.1% | 20.417 | 17.6% | 10.3% | 15.4% | 19.1% |
| CH | 58.3% | 58.3% | 58.3% | 58.3% | 58.3% | 58.3% | 58.3% | 58.3% | 58.3% |

**G:** Group, **P:** Patients, **C:** Control, **HT:** Hypertension, **FH:** Family history, **HL:** Hyperlipidemia, **Het:** Heterozygous, **Hom:** Homozygous, **MTHFR:** Methylene tetrahydrofolate reduclease, **CH:** Cournpound Heterozygous, **NV:** No variation, **ACE:** Angiotensin Converting Enzyme, **PIA:** Plasminogen Activator Inhibitor-I, **NSA:** No Significant Association, * = Statistically significant.
pressure. It was reported that the insertion deletion polymorphism (rs4646994) was significantly related with MI in different ethnic populations\textsuperscript{11-13}. Some studies have shown a significant\textsuperscript{14-16}, while others a nonsignificant association between FVL mutation and MI\textsuperscript{17-19}. Matthijs B et al.\textsuperscript{20} found no correlation between MI risk and prothrombin G20201A and FVL mutations. The prothrombin G20201A mutation has been related with elevated prothrombin levels. The G20210A polymorphism of FII gene was related with an overall nearly twofold increased risk of STEMI in young carriers while FVL showed no relation\textsuperscript{21}. However, other studies reported a correlation between Prothrombin G20210A Mutation and MI\textsuperscript{22,23}.

A significant relation between increased and decreased MI risk and both homozygosity for the fibrinogen 455A allele and PAI-1 4G allele were reported, respectively\textsuperscript{20}. A significant association between Fibrinogen $\beta$-Chain G455A polymorphism and the lower risk of MI according to recessive model but lack of any significant relation according to the dominant model was reported\textsuperscript{23}. FXIII has a fundamental function in the thrombus formation. Significant decrease in FXIII antigen after MI other than different FXIII genotypes (L34-carriers had higher FXIII activity) was reported\textsuperscript{24}.

There are some inconsistencies in the results of studies about the relation between MI risk and genetic variations of inherited thrombophilia factors. These inconsistencies may be caused by ethnicity, design of study, sample size, inclusion or exclusion criteria in the selection of individuals etc.

Based on our results, when distribution of inherited thrombophilia factors according to the severity of vessel diseases to be considered, statistically significant differences were detected for MTHFR A1298C and Factor V Cambridge G1091C.

The occurrence of single vessel disease especially in the left anterior descending coronary artery is highly prevalent in patients with ACS25. Thrombosis of multiple coronary arteries seen in a patient with STEMI is an unusual angiographic finding but it can cause fatal complication\textsuperscript{26}. Synchronous multivessel coronary thrombosis can occur secondary to different etiologies (e.g. cocaine abuse, idiopathic thrombocytopenic purpura, coronary artery spasm, increased tendency to thrombosis, anti-thrombin III deficiency, as well as thrombophilias such as antiphospholipid antibodies, FVL deficiency, and essential thrombocytosis)\textsuperscript{27}. However, the underlying mechanism still remains unclear in most of these patients. A young man with coronary arterial thrombosis caused by protein C deficiency and heterozygous FVL was reported\textsuperscript{28}.

When the combination of inherited thrombophilia factors and other risk factors for STEMI to be considered, significantly higher MTHFR A1298C, Factor V Leiden G1691A, PAI and ACE gene variations were detected in smoker MI patients rather than smoker control patients (p<0.05). All of significantly higher Factor XIII, PAI and ACE gene variations were found in MI patients with HT rather than the control patients with HT (p<0.05). Also both PAI and ACE gene variations were significantly higher in MI patients with FH than the control patients with FH, too (p<0.05). Additionally, significantly higher PAI gene variation was found in MI patients with HL than the control patients with HL (p<0.05).

Smokers with D allele in ACE gene had increased risk for STEMI than nonsmokers. It was demonstrated that D allele and smoking are related with elevated levels of angiotensin II that have been shown to increase the generation of superoxide anions and degradation of nitric oxide resulting in endothelial dysfunction\textsuperscript{9}. Also, it was shown that FVL carriers who smoked had increased risk for MI\textsuperscript{20}.

Similar to our study, it was reported that smoking, dyslipidemia, obesity, family history of atherothrombotic disease are the major risk factors of the STEMI\textsuperscript{29-31}. Also smoking, dyslipidemia, obe-
sity, hypertension, and diabetes mellitus are increased risk factors for STEMI. When the compound heterozygous or homozygous carriers to be considered, significantly higher compound heterozygous or homozygous carriers were detected in patients with all risk factors of DM, HT, HL, FH and smoking than the control patients with all the same risk factors (p<0.05). Furthermore, in the current study frequencies of diabetes mellitus, hypertension, hyperlipidemia, obesity, and family history of cardiovascular disease were significantly higher and HDL-cholesterol levels were significantly lower in STEMI group than the control group.

Study limitations
This study was done with relatively few participants selected after investigation of broad series with inherited thrombophilia. For a better understanding and management of the disease, it is important to examine wide series with hereditary thrombosis and their relationship with other risk factors that play an important roles in the development of the disease.

CONCLUSION
In addition to modifiable risk factors, hereditary thrombophilias including MTHFR A1298C, FactorXIII, ITGB, ACE, Factor V Cambridge G1091C and homozygous or compound heterozygous gene variations of the inherited thrombophilia should be considered in STEMI patients. Based on our screening of various gene variations, MTHFR A1298C, Factor V Leiden G1691A, PAI and ACE genes in smokers with STEMI; Factor XIII V34L, PAI and ACE genes in individuals with STEMI and HT; PAI and ACE genes in individuals with STEMI and FH; PAI gene variations in individuals with STEMI and HL could be considered as markers for STEMI risk. It can be said that hereditary thrombophilia factors show promise in the prevention and management of STEMI when supported by studies in larger case series.

Acknowledgements: We thank the participants for their contribution.

REFERENCES
1. World Health Organisation. Cardiovascular diseases. https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1 (Available on 23 November 2020)
2. Antman EM, Braunwald E. ST Elevasyonlu Miyokardiyal Infarktus: Patoloji, Patofizyoloji ve Klinik Özellikler. In Zipes PD, Libby P, Bonow RO, Braunwald E. editors. Braunwald’s Heart Disease [Braunwald Kalp Hastalıkları]. Aslanger E, Sirinoğlu I. translator. İstanbul: Nobel Tip Kitap Evi; 2008. Volume 2, p.1144.
3. Eroz R, Damar İH, Kılıçaslan O. Thrombosis risk of Alport syndrome patients: evaluation of cardiological, clinical, biochemical, genetic and possible causes of inherited thrombophilia and identification of a novel COL4A3 variant. Blood Coagul Fibrinolysis. 2020;31:264-9. [CrossRef]
4. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72:2231-64. [CrossRef]
5. Rallidis LS, Gialeraki A, Tsarebolos G, Tsalavoutas S, Ralli M, Iliodromitis E. Renin-angiotensin system gene polymorphisms and risk of premature ST elevation myocardial infarction. J Thromb Thrombolysis. 2017;44(2):267-73. [CrossRef]
6. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227-39. [CrossRef]
7. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1-39.e14. [CrossRef]
8. Isordia-Salas I, Leaños-Miranda A, Sainz IM, Reyes-Maldonado E, Borrayo-Sánchez G. Association of the PlasmaARGIN Activator Inhibitor-1 Gene 4G/5G Polymorphism With ST Elevation Acute Myocardial Infarction in Young Patients. Revista Española de Cardiología. 2009;62:365-72. [CrossRef]
9. Isordia-Salas I, Alvarado-Moreno JA, Jiménez-Alvarado RM, et al. Association of renin-angiotensin system genes polymorphisms and risk of premature ST elevation myocardial infarction in young Mexican population. Blood Coagul Fibrinolysis. 2018;29:267-74. [CrossRef]
10. Isordia-Salas I, Trejo-Aguilar A, Valadés-Mejía MAG, et al. C677T Polymorphism of the 5,10 MTHFR Gene in Young Mexican Subjects with ST-Elevation Myocardial Infarction. Arch Med Res. 2010;41:246-50. [CrossRef]
11. Al-Hazzani A, Daoud MS, Ataya FS, Fouad D, Al-Jafari AA. Renin-angiotensin system gene polymorphisms among Saudi patients with coronary artery disease. J Biol Res (Thessalon). 2014;21:8. [CrossRef]
12. Hamelin BA, Zakrzewski-Jakublak M, Robitalle NM, Bogaty P, Labbé L, Turgeon J. Increased risk of myocardial infarction associated with angiotensin-converting enzyme gene polymorphism is age dependent. J Clin Pharmacol. 2011;51:1286-92. [CrossRef]
13. Freitas AI, Mendonça I, Brion M, et al. RAS gene poly-
morphisms, classical risk factors and the advent of coronary artery disease in the Portuguese population. BMC Cardiovasc Disord. 2008;8:15. [CrossRef]
14. Rosendaal FR, Siscovick DS, Schwartz SM, et al. Factor V Leiden (resistance to activated protein C) increases the risk of myocardial infarction in young women. Blood. 1999;94:46-51. [CrossRef]
15. Ardissino D, Mannucci PM, Merlini PA, et al. Prothrombotic genetic risk factors in young survivors of myocardial infarction. Blood. 1999;94:46-51. [CrossRef]
16. Junker R, Heinrich J, Schulte H, et al. Plasminogen activator inhibitor-1 4G/5G-polymorphism and factor V Q506 mutation are not associated with myocardial infarction in young men. Blood Coagul Fibrinolysis. 1998;9:597-602. [CrossRef]
17. Feng Y, Draghi A, Linfert DR, Wu AH, Tsongalis GJ. Polymorphisms in the genes for coagulation factors II, V, and VII in patients with ischemic heart disease. Arch Pathol Lab Med. 1999;123:1230-5.
18. Gowda MS, Zucker ML, Vacek JL, et al. Incidence of factor V Leiden in patients with acute myocardial infarction. J Thromb Thrombolysis. 2000;9:43-5. [CrossRef]
19. Makris TK, Krespi AN, Hatzizacharias AN, et al. Resistance to activated protein C and FV Leiden mutation in patients with a history of acute myocardial infarction or primary hypertension. Am J Hypertens. 2000;13:61-5. [CrossRef]
20. Boekholdt SM, Bijsterveld NR, Moons AH, Levi M, Böller HR, Peters RJ. Genetic Variation in Coagulation and Fibrinolytic Proteins and Their Relation With Acute Myocardial Infarction: A Systematic Review. Circulation. 2001;104:3063-8. [CrossRef]
21. Rallidis LS, Galaraki A, Tsireblos G, Tsalavoutas S, Rallidis M, Iliodromitis E. Prothrombotic genetic risk factors in patients with very early ST segment elevation myocardial infarction J Thromb Thrombolysis. 2017;44:267-73. [CrossRef]
22. Croft SA, Daly ME, Steeds RP, Channer KS, Samani NJ, Hampton KK. The prothrombin 20210A allele and its association with myocardial infarction. Thromb Haemost. 1999;81:861-4. [CrossRef]
23. Croft F, Hamsten A, Blomback M, Humphries S. The role of beta-fibrinogen genotype in determining plasma fibrinogen levels in young survivors of myocardial infarction and healthy controls from Sweden. Thromb Haemost. 1993;70:915-20. [CrossRef]
24. Gemmati D, Federici F, Campo G, et al. Factor XIIIa-V34L and factor XIIIb-H95R gene variants: effects on survival in myocardial infarction patients. Mol Med. 2007;13:112-20. [CrossRef]
25. Puricel S, Lehner C, Oberhansli M, et al. Acute coronary syndrome in patients younger than 30 years--etiology, baseline characteristics and long-term clinical outcome. Swiss Med Wkly. 2013;143:w13816. [CrossRef]
26. Kim S, Seol SH, Park DH, et al. Simultaneous multiple coronary arteries thrombosis in patients with STEMI. J Geriatr Cardiol. 2015;12:241-3.
27. Kanel Y, Janardhanan R, Fox JT, Gowda RM. Multivessel coronary artery thrombosis. J Invasive Cardiol.2009;21:66-8. [PubMed] [Google Scholar]
28. Hubert A, Gutret P, Leurent G, Martins RP, Auwret F, Bedossa M. Myocardial infarction and thrombophilia: Do not miss the right diagnosis! Revista Portuguesa de Cardiologia. 2018;89.e1-89.e4. [CrossRef]
29. Jamil G, Jamil M, Alkhazraji H, et al. Risk factor assessment of young patients with acute myocardial infarction. Am J Cardiopath. 2003;3:170-4.
30. Luo E, Wang D, Yan G, et al. High triglyceride-glucose index is associated with poor prognosis in patients with acute ST-elevation myocardial infarction percutaneous coronary intervention. Cardiovasc Diabetol. 2019;18:150. [CrossRef]
31. Haller PM, Boeddinghaus J, Neumann JT, et al. Performance of the ESC 0/1-h and 0/3-h algorithm for the rapid identification of myocardial infarction without ST-elevation in patients with diabetes. Diabetes Care. 2020;43:460-7. [CrossRef]