THE RELATION BETWEEN SEASONAL VARIATION AND MORTALITY IN PATIENTS WITH ST ELEVATION MYOCARDIAL INFARCTION

TURGAY ISIK[1], ERKAN AYHAN[2], HUSEYIN UYAREL[3], ZEKI YÜKSEL GÜNAYDIN[4], OSMAN BEKTAS[4], AHMET KARAGOZ[5]
[1]Department of Cardiology, Balikesir University, School of Medicine, Balikesir - [2]Department of Cardiology, Medical Park Hospital, Bursa - [3]Department Of Cardiology, Bezmialem University, School of Medicine, Istanbul - [4]Department of Cardiology, Ordu University, School of Medicine, Ordu - [5]Department Of Cardiology, Giresun University, School of Medicine, Giresun, Turkey

ABSTRACT

***Aim**: Acute vascular events show a circadian rhythm and daily variation. Previous studies demonstrated that ST segment elevation myocardial infarction (STEMI) increases in winter season; however, the prognosis of the patients that presented at different seasons has not been investigated yet. In this study we investigated the seasonal mortality variation of the patients who underwent primary percutaneous coronary intervention (PCI) for STEMI.*

***Materials and methods**: We reviewed 2644 consecutive patients treated with primary PCI for STEMI. The date of STEMI was obtained from medical record. Patients were divided into groups depending on the season to the applicant. Group I (Autumn) had 570 (21.6%) patients, Group II (Winter) had 807 (30.5%) patients, Group III (Spring) had 734 (27.8%) patients and Group IV (Summer) had 533 (20.2%) patients.*

***Results**: Age, sex and most of cardiovascular risk factors and angiographic features were comparable among groups. When compared to the group IV, in hospital reinfarction (re-MI) incidence was significantly higher in group II (3.2% vs 0.8%, p: 0.009). There were no differences between groups for in hospital and long term mortality, long term re-MI, target vessel revascularization and major adverse cardiac events (MACE).*

***Conclusion**: This study showed that there were no seasonal variation in hospital and long-term mortality, long term re-MI and MACE after primary PCI for STEMI. Besides, in hospital re- MI incidence was significantly higher in winter when compared to the summer.*

***Key words**: Seasonal variation, ST segment elevation myocardial infarction, mortality, primary PCI.*

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Introduction

Coronary artery disease is the most common cause of the mortality and it constitutes 12.8% of all deaths(1). Over the years, ST segment elevation myocardial infarction (STEMI) incidence has become decreased and non-STEMI has become increased. Many factors are associated with STEMI mortality such as age, Killip class, time to therapy, diabetes mellitus (DM), number of diseased vessels, left ventricular ejection fraction (LVEF) and treatment modality. In-hospital mortality of STEMI ranges between 6% and 14%(2). In-hospital and long term mortality of STEMI have been significantly decreased after primary percutaneous coronary intervention (PCI)(3, 4). Despite all these improvement, as 12% of the STEMI patients die within six-months, prognostic factors and improved quality of the health care of the patients with high risk factors have been gained importance.

There appears to be a circadian rhythm and daily variation in certain acute vascular events, including stroke, pulmonary thromboembolism, myocardial infarction (MI), and sudden cardiac death(5-8). Even if studies from different regions show different results, most of them indicated a winter season acute MI increment(9-12). Marchant et al revealed that acute MI is more common in winter and as well as on colder days. They suggested that environmental temperature may play an important part in the pathogenesis of acute MI. In this study hospital admission rate showed significant seasonal variation with more admissions during winter months when compared to the summer months. Thus 30.5% of the total study group presented in the three months from December to February[11]. The seasonal difference of acute MI was thought to be related to temperature, sunlight, biological circannual rhythm, metabolic and homeostatic changes, infections and life style factors[13]. However, whether most of the studies showed that the acute MI prevalence increases during the winter season, it is not known if seasonal differences affect the prognosis of these patients. In this study we investigated any seasonal variation for mortality in 2644 patients who underwent primary PCI for STEMI.

Materials and methods

Patient populations

Primary PCI was performed in 2825 patients admitted with the diagnosis of acute MI within 12 hours from the onset of chest pain. The diagnosis of acute MI required the presence of at least 2 of the following 3 criteria:

• ST- segment elevation or new onset of complete left bundle-branch block on an electrocardiogram consistent with acute MI;

• symptoms of myocardial ischemia lasting for 20 minutes;

• transient increase in cardiac enzymes to more than 2-folds the normal laboratory value. A total of 181 patients were excluded from the study because no percutaneous treatment was undertaken (medical treatment or coronary by-pass surgery). The population consisted of 2644 patients, who were evaluated retrospectively.

Analysis of Patient Data

A clinical history of risk factors such as age, gender, DM, hypertension, hypercholesterolemia, cigarette smoking, MI history, PCI or bypass history was determined from the medical records. A 12-lead electrocardiogram (ECG) was recorded in each patient just after the hospital admission, and the MI type was also recorded from the ECGs.

The weather in city, has 4 distinct season. The temperature changes dramatically between the seasons. The Autumn season (Group I patients) is described as the period of time from September to the last day of November. The winter season (Group II patients) is described as the period of time from December of a year to the last day of February of the following year. The Spring season (Group III patients) is described as a period of time from March to the last day of May. The summer season (Group IV patients) is described as a period of time from June to the last day of August.

After primary PCI, the global LVEF was measured by transthoracic echocardiography using a system V (GE Vingmed Ultrasound, Horton, Norway), with a 2.5-MHz phased-array transducer. The LVEF was measured using the modified Simpson's rule[14].

Coronary angiography and stenting

All patients received chewable acetyl-salicylic acid (300 mg, unless contraindicated) and clopidogrel (300 mg loading dose) prior to the coronary angiography. Emergency coronary angiography and stenting were performed through the percutaneous femoral approach. After visualizing the left and right coronary arteries, 2.5 mg of isosorbide dinitrate was selectively injected into the infarct related artery (IRA) to rule out possible coronary spasm. Angiographic assessments were made at the treating hospital by visual assessment. IRA was graded according to the Thrombolysis In Myocardial Infarction (TIMI) classification[15]. Primary coronary stenting was performed only for IRA. Stents were deployed according to the standard techniques. All the patients received unfractionated heparin intravenously during the procedure (70 U/kg bolus), and heparin infusion (to maintain the activated partial prothrombin time between 80 and 150 seconds), or subcutaneous low-molecular-weight heparin (1 mg/kg twice a day) was restarted immediately after application of pressure bandage. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. After the stenting, all the patients were prescribed a lifelong acetyl-salicylic acid (100 mg daily) regimen, and clopidogrel (75 mg daily) was prescribed for at least one month. Concomitant medical treatment with β-blockers, angiotensin-converting enzyme inhibitors, and statins followed according to the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA).

Definition

Three-vessel disease was defined as the presence of more than 50% stenosis in three major epicardial coronary arteries. Time to reperfusion was measured as the time from the onset of symptoms to the coronary reperfusion acquired with balloon inflation. Patients were also evaluated according to the Killip clinical examination classification[16]. Patients with DM were defined those with documented DM using either oral hypoglycaemic agents or insulin treatment on admission. Hypercholesterolemia was defined as total cholesterol of ≥200 mg/dl or use of cholesterol-lowering agents.

Cardiovascular mortality was identified as unexplained sudden death and mortality associated with acute MI, heart failure, or arrhythmia. Reinfarction (re-MI) was defined when ST elevation ≥0.1 mV recurs, or new pathognomonic Q waves appear, in at least two contiguous leads, particularly when associated with ischaemic symptoms for 20 min or longer that occurs within 28 days of an incident- or recurrent MI. Target vessel revascularization (TVR) was defined as presence of a need for PCI or coronary surgery because of restenosis or reocclusion of the IRA. Advanced heart failure was described as a heart failure of at least Class III severity based on the New York Heart Association functional classification system. Major adverse cardiac events (MACE) were defined as cardiovascular death, re-MI, repeat TVR. Only cardiovascular mortality was recorded.

Statistical analysis

Quantitative variables were expressed as mean value ± SD, and qualitative variables were expressed as percentage. To compare parametric continuous variables, the Student's t test or analysis of variance were used; to compare non-parametric continuous variables, the Mann-Whitney U or Kruskall-Wallis tests were used. To compare categorical variables the chi-square test was used. A P value of <0.05 was considered statistically significant. All statistical studies were carried out using the statistical package for the social sciences (SPSS) program (version 15.0; SPSS, Chicago, Illinois, USA).

Results

In total, 2644 patients were enrolled in the study (mean age 56.7 ± 11.9 years, 82.8 % males). Group I (56.5±11.9, Male: 82.3%) had 570 (21.6%) patients, group II (57.3±12.0, Male: 83.8%) had 807 (30.5%) patients, group III (57.0±11.9, Male: 83.1%) had 734 (27.8%) patients and group IV (55.4±11.4, Male: 81.2%) had 533 (20.2%) patients. The groups were similar in term of the sex and age. In group IV the anterior MI was significantly more frequent than the group III (53,3% vs 45%, p:0,04), and the hyperlipidaemia in group II was significantly higher than group IV (40,5% vs 33,1%, p:0,003). The other baseline clinical characteristics are shown in Table 1.

Variable	Group 1 (n=570)	Group 2 (n=807)	Group 3 (n=734)	Group 4 (n=533)	P Value
Age, years	56.5±11.9	57.3±12.0	57.0±11.9	55.4±11.4	0.07
Male, n(%)	469(82.3)	676(83.8)	610(83.1)	433(81.2)	0.66
Anterior MI, n(%)	270(47.4)	412(51.1)	331(45.1)	284(53.3)	0.01*
Hyperlipidemia, n(%)	193(36.4)	294(40.8)	234(34.6)	165(33.1)	0.03**
Diabetes mellitus, n(%)	134(24.1)	200(25.3)	178(24.9)	142(27)	0.73
Current smoker, n(%)	336(62.9)	465(63.9)	396(58.6)	314(62.7)	0.19
Hypertension, n(%)	227(41.3)	324(43.4)	291(42.4)	193(37.5)	0.19
GFR<60, n(%)	85(12)	93(11.9)	85(12)	70(13.3)	0.85
By-pass history, n(%)	12(2.1)	18(2.2)	29(4)	19(3.6)	0.1
PCI history, n(%)	37(6.5)	63(7.9)	63(8.7)	47(8.9)	0.43
MI history, n(%)	55(9.7)	83(10.5)	88(12.2)	60(11.4)	0.51
Reperfusion time, h	3.19±2.25	3.29±2.40	3.39±2.64	3.12±2.24	0.8
CK-MB, IU/L	220.5±170.6	230.3±193.4	211.7±192.4	215.0±169.5	0.08
Killip >1, n(%)	44(10.7)	61(11.9)	54(11)	39(9.8)	0.8
Anemia at admission, n (%)	143(25.8)	200(26)	172(24.5)	135(26.1)	0.9
Postprocedural EF, %	47.2±10.3	46.8±11.6	48.2±10.9	46.7±12.2	0.31

Table 1: Baseline characteristics of study patients.
Mean values (SD) and % (n) are reported for continuous and categorical variables, respectively. EF: Ejection Fraction, CAD: Coronary Artery Disease, GRF: Glomerular Filtration Rate, MI: Myocardial Infarction, PCI: Percutaneous Coronary Intervention, CK-MB: creatine kinase MB, Group 1: Autumn season, Group 2: Winter season, Group 2: Spring season, Group 4: Summer season.
**p value was singnificant only between in group 3 and group 4 (p: 0.04).*
***p value was singnificant only between in group 2 and group 4 (p: 0.03).*

Angiographic and procedural characteristics are shown in Table 2. The groups were similar in terms of the culprit lesion (only in group IV the left anterior descending artery lesion was significantly more than the group III (53,3% vs 45.1%, p:0,04)), pre-TIMI flow grade, proximal lesion, trivessel disease, use of stents, length and diameter of stents, usage of drug eluting stent, tirofiban and the success rate of the procedure. Angiographic and procedural characteristics are shown in Table 2.

Variable	Group 1 (n=570)	Group 2 (n=807)	Group 3 (n=734)	Group 4 (n=533)	P Value
Culprit lesion, n(%)					
LMCA	0(0)	2(0.2)	4(0.5)	0(0)	0.12
LAD	275(48.3)	412(51.1)	331(45.1)	284(53.3)	0.02*
Lcx	84(14.7)	96(11.9)	101(13.8)	66(12.4)	0.41
RCA	204(35.8)	291(36.1)	291(39.1)	180(33.8)	0.17
Others	8(1.4)	5(0.6)	7(1)	3(0.6)	0.37
Pre TIMI grade, n(%)					
0/1	491(86.3)	708(88.3)	654(89.1)	464(87.2)	0.44
2	54(9.5)	57(7.1)	56(7.6)	44(8.3)	0.42
3	24(4.2)	37(4.6)	24(3.3)	42(4.5)	0.56
Proximal lesion, n(%)	307(54.3)	440(54.9)	370(50.7)	298(56.2)	0.2
Three vessel disease, n(%)	133(23.5)	217(27)	202(27.5)	133(25)	0.34
Success of procedure, n(%)	499(87.5)	724(89.7)	656(89.4)	491(91.9)	0.12
DES, n(%)	16(3.5)	20(3.1)	17(2.9)	13(3)	0.85
Stent length, mm	19.27+6.52	19.35+6.91	19.38+6.64	19.02+6.65	0.8
Stent diameter, mm	3.10+0.34	3.11+0.33	3.11+0.35	3.11+0.34	0.92
Tirofiban administe-red, n (%)	257(46.1)	363(46.7)	366(51.4)	258(49)	0.19
Procedure, n(%)					
PTCA	88(16.4)	124(15.9)	109(15.5)	77(15)	0.93
PTCA+Stent	133(24.7)	212(27.2)	178(25.3)	132(25.7)	0.74
Stent	317(58.9)	442(56.8)	417(59.2)	305(59.3)	0.73

Table 2: Angiographic and Procedural Characteristics of Study Patients.

Mean values (SD) and % (n) are reported for continuous and categorical variables, respectively. DES: Drug Eluting Stent, LMCA: Left Main Coronary Artery, LAD: Left Anterior Descending, Lcx: Left Circumflex, PTCA: Percutaneous Coronary Angioplasty, RCA: Right Coronary Artery, TIMI: Thrombolysis In Myocardial Infarction, Group 1: Autumn season, Group 2: Winter season, Group 2: Spring season, Group 4: Summer season.

** P value was singnificant only between in group 3 and group 4 (p: 0.004).*

In hospital follow up, there was no significant difference between groups in regard to the incidence of mortality (6.1%, 5%, 5.6% and 6% respectively, p: 0.77), TVR (3.9%, 5.6%, 4.2%, and 3.4% respectively, p: 0.22), MACE (9.3%, 10.3%, 9.1% and 8.6% respectively, p: 0.76) and advanced heart failure (11.4%, 14.6%, 14.3% and 15.2% respectively, p: 0.25). However, group II had a significantly higher re-MI incidence than group IV (3.2% vs 0.8%, p: 0.009) (Figure 1). During the long term follow-up (mean 22 months) there was no significant difference between groups in regard to the incidence of mortality (6.5%, 4.4%, 6.3% and 4.7% respectively, p: 0.23), re-MI (7.4%, 9.2%, 12% and 8.2% respectively, p:0.06), TVR (18.2%, 19.8%, 19.9% and 14.8% respectively, p:0.13), MACE (25.4%, 25.5, 27.2% and %20.9 respectively, p: 0.12) and advanced heart failure (7.4%, 9.3 %, 8.1% and 10.2% respectively, p:0.44) (Table 3, Figure 2).

Discussion

The present study results revealed that, although re-MI incidence was comparable in long term, in-hospital re-MI incidence was significantly higher in winter when compared to the summer. Secondly, there was not any seasonal variation in hospital and long-term mortality, TVR, MACE and advanced heart failure after primary PCI for STEMI.

In previous studies it has been reported that acute MI are more likely to occur in winter[11,12,17]. Spencer et al showed an excess of 53% cases in winter compared to summer[12]. Manfrenidi et al reported acute MI was most frequent in winter and least in summer. The highest number of cases was recorded in January and the lowest in July[18]. Spielberg et al showed MI occurred more during the winter from January to March compared with other seasons. There are inconsistent studies. Mahmoud et al showed coronary stent thrombosis was more likely to occur in the summer months[10]. The probable causes of the conflicting results of this study are the length of months not equal in that region, and the wide variations in weather conditions may occur within any given month. Although most of the STEMI patient admitted to the hospital during winter and least patient during summer in this study, there is a wide variation of patient number that can serve from the hospital between seasons (not the stable population). That is why we did not evaluate this seasonal difference. Additional this issue has been extensively discussed by larger studies previously[11,12].

Although there are many studies showing the seasonal cardiovascular events prevalence changes, there is not enough studies showing how this seasonal differences affects the prognosis of the patients. Rumana et al reported that the incidence of acute MI and fatality risk within 28 days of subjects who suffered an acute MI was higher during winter and spring season[19].

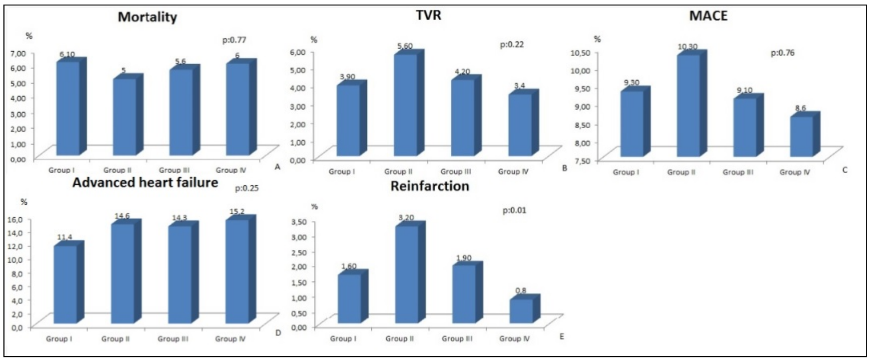

Fig 1: In hospital follow up mortality, TVR, MACE, Advanced heart failure and reinfarction (P value was singnificant only between in group 2 and group 4 for reinfarction, p: 0.009). (TVR: Target vessel revascularization, MACE: Major adverse cardiac events, Group I: Autumn, Group II: Winter, Group III: Spring, Group IV: Summer).

In-hospital cardiac events and complications	Group 1 (n=570)	Group 2 (n=807)	Group 3 (n=734)	Group 4 (n=533)	p Value
In-hospital mortality, n (%)	35(6.1)	40(5)	41(5.6)	32(6)	0.77
Reinfarction, n (%)	9(1.6)	26(3.2)	14(1.9)	4(0.8)	0.01*
Target-vessel revascularization, n (%)	22(3.9)	45(5.6)	31(4.2)	18(3.4)	0.22
MACE, n (%)	53(9.3)	83(10.3)	67(9.1)	46(8.6)	0.76
Advanced heart failure, n(%)	65(11.4)	118(14.6)	105(14.3)	81(15.2)	0.25
Long term cardiac events and complications					
Mortality, n (%)	34(6.5)	33(4.4)	43(6.3)	23(4.7)	0.23
Reinfarction, n (%)	34(7.4)	76(12)	53(9.2)	36(8.2)	0.06
Target-vessel revascularization, n (%)	84(18.2)	127(19.8)	115(19.9)	65(14.8)	0.13
MACE, n (%)	120(25.4)	165(25.5)	161(27.2)	93(20.9)	0.12
Advanced heart failure, n (%)	34(7.4)	59(9.3)	47(8.1)	45(10.2)	0.44

Table 3: In-hospital and long term cardiac events.
% (n) are reported for categorical variables. MACE: Major adverse cardiac events (cardiovascular death, reinfarction, target–vessel revascularization). Group 1: Winter season, Group 2: Summer season.
** P value was singnificant only between in group 2 and group 4 (p: 0.009).*

Conversely De luca et al. reported that absence of seasonal variation in myocardial perfusion, enzymatic infarct size, ejection fraction and 1 year- mortality in patients with STEMI treated with primary PCI[20]. Additionally, Kloner et al showed larger infarct size in winter season in patients who were treated with thrombolysis or who were not. There are some controversial results in that study. Although there was no difference in TIMI flow, a significant seasonal variation in infarct size was observed, with larger infarcts in winter season. Although the infarct size is larger during winter season, there is no difference of the in-hospital outcomes[21]. In this study we found no difference for infarct size (with LVEF and creatine kinase MB) and the clinical follow up of the patients in different groups. The similarity of the patients' prognosis (except the in-hospital re-MI) may be related to the similar demographic and angiographic features, reperfusion time, infarct size, and optimal reperfusion ratios (TIMI 3). The in-hospital re-MI was seen more during winter season and this might be related to the thombojenity that is increased during this season. And also probably as a result of availability of primer angioplasty for 7days/24 hours in our hospital this re-MI does not result in an increase of mortality. In study of Kloner at al the infarct size was wide during winter season. This might be related to the platelet aggregation and fibrinogens' seasonal changes that causes the fibrinolytic response[22, 23].

However, even if we found similar prognosis in the patient that undergone the primary PCI in different seasons, there are studies indicated worse prognosis and increased incidence during the winter season. They suggested that physiologic variables with seasonal rhythmicity might be associated to the seasonal deviations in acute MI occurrence and its outcomes. The reasons underlying the higher occurrence of acute MI and poor prognosis in winter have remained controversial, but investigators have mostly pointed to cold[24] (associated with increase in platelets, red blood cell count, blood viscosity and fibrinogen)[22,23], biological factors (such as blood pressure[25], serum cholesterol and triglyceride levels[26,27], fibrinogen and activated factor 7 levels[26] and respiratory infections causing damage

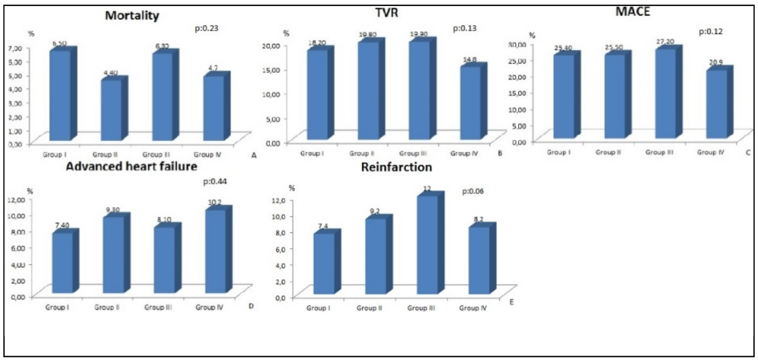

Fig 2:Long term follow-up mortality, TVR, MACE, Advanced heart failure and reinfarction. (TVR: Target vessel revascularization, MACE: Major adverse cardiac events, Group I: Autumn, Group II: Winter, Group III: Spring, Group IV: Summer).

to vessel walls[28]so might trigger MI and effect its prognosis. In another study, Zipes et al suggested that due to alterations in the biological clocks the mortality due to cardiovascular events might increase in winter. This biological clock is located in the suprachiasmatic nuclei and its rhythm is determined by day-night alternation that is, by light darkness cycles. The secretion of cortisol, tissue plasminogen activator, pro-inflammatory cytokines are regulated by these cycles. It might be that the increase in mortality may be as a result of the reduction in the number of solar light hours in the winter modulates these pathophysiological processes, instead of winter cold[29]. Additionally, as a result of a high rate of re-entry into professional life can be assumed for these months, the transition from low stress to higher stress work may be a contributory cause of the increases in vascular events occurrence. Also it should not be forgotten that during the winter season due to the weather condition it may takes longer time to reach the hospital and this may result in a wider infarct size and worse prognosis due to increased reperfusion time. The studies that claimed the thrombotic events increased during summer season, suggested that passive heating in the summer may cause activation of sympathetic nervous system and increased heart rate and thus may explain higher rate of acute coronary syndrome in the summer[10].

Limitations

Several limitations need to be kept in mind when interpreting the results of this study. First, this study has a retrospective design that per se is a well-known limitation. Second in this study we did not evaluate seasonal STEMI frequency due to not the stable population. Thirdly, the probable reason why the re-MI frequency increases during the winter season is the probable increase of the coagulation factors (such as fibrinogen and other coagulation factors), however this suggestion has not been supported by any laboratory data.

Conclusion

This study showed that absence of any seasonal variation in hospital and long-term mortality after primary PCI for STEMI.

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Correspoding author
ERKAN AYHAN, MD.
Department of Cardiology, Medical Park Hospital, Hasim Iscan St. No. 1, Osmangazi, 16220 Bursa
(Turkey)