

Evaluation of Clinical Features including the frequency of Familial Hypercholesterolemia, and 2-Year Cardiovascular Outcomes in Patients with Early Acute Coronary Syndrome: Real-Life Data from a Retrospective Cohort

📧 Meral Kayikcioglu, 📧 Bahadir Alan, 📧 Burcu Yağmur

Ege University Medical Faculty, Department of Cardiology, Izmir, Turkey

ABSTRACT

Keywords

Acute coronary syndrome;
age of onset;
familial
hypercholesterolemia;
mortality;
patient outcomes;
early cardiovascular
disease



© 2023 The Authors
Published by SITeCS

Objective: This retrospective study, based on real-world data, aimed to evaluate the clinical characteristics and 2-year cardiovascular outcomes in patients presenting with early acute coronary syndrome (ACS) in comparison with older patients in a tertiary healthcare center.

Methods: Information including at least 2-year endpoint data after the index ACS event was retrieved from hospital records. Patients without available follow-up data were contacted by phone-calls. Age limit for early cardiovascular disease was considered <55 years for men and <60 years for women.

Results: Of 985 consecutive ACS patients (770 men; age range, 21-93 years) 361 (36.6%) met the definition of early cardiovascular disease in terms of age at the index event. The following parameters were observed more frequently in the young-age group: smoking, a body mass index ≥ 30 kg/m², high total cholesterol level, high triglyceride level, low high-density lipoprotein cholesterol (HDL-C) level, and family history of coronary artery disease (CAD). The frequency of familial hypercholesterolemia (FH) was 7.6% and was higher in the young group (15.5%) than in the elderly group (3%) ($p < 0.001$). During the follow-up period, the risk predictors for cardiovascular events were the index event (ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction) and the presence of hypertension, and the risk predictors for mortality were female sex, older age, in-hospital cardiovascular complications.

Conclusion: In this retrospective ACS cohort of a single center from Turkey, a very high rate of early ACS (36.6%) was observed. Compared to older patients, young ACS patients were more likely to be smokers, more obese, less diabetic and less hypertensive. High total cholesterol, high triglycerides, low HDL-C levels, high non-HDL-C, family history of CAD, and FH were also observed more frequently in the young ACS group. The high prevalence of FH may be a major factor in the high prevalence of premature ACS in this population. Both the in-hospital and 2-year follow-up mortality rates were significantly lower in the young group.

Received 8 May 2023; accepted 2 August 2023

Introduction

The incidence of coronary artery disease (CAD) increases with age, and generally atherosclerosis is considered a disease of old age. Acute myocardial infarction (MI) is not a common occurrence at young ages and its frequency has been reported between 5% and

13%, depending on the cut-off age used for defining early age [1-3]. Although data are limited, the incidence of early CAD has been reported to be unexpectedly high in Turkey. The EUROASPIRE-IV study reported a 12% overall incidence of MI in patients <50 years in Europe; however, in Turkish arm of the same study, this rate was reported to be 19% [4]. The disease course, complications and out-

Corresponding Author

Meral Kayikcioglu: meral.kayikcioglu@gmail.com

comes differ significantly in young as compared with older people. This retrospective study, based on real-life data, aimed to evaluate the clinical characteristics and 2-year cardiovascular (CV) outcomes in patients presenting with an early acute coronary syndrome (ACS) (<55 years for males and <60 years for females) compared with older patients in a tertiary healthcare center.

Methods

Patients

The present study was designed as a retrospective cohort study in a tertiary healthcare center. All consecutive patients admitted to the Cardiology Department of Ege University School of Medicine with a diagnosis of ACS [unstable angina pectoris (UAP), ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation myocardial infarction (NSTEMI)] were included in a 6-month follow-up period. Patient information was retrospectively retrieved from archived medical records and from the electronic data system of the hospital. At least 2-year outcome data of patients after the index ACS event were obtained from the same medical data recording system of the hospital. Information of patients for whom follow-up data were not available was obtained via phone calls.

The study inclusion criteria were as follows:

- i) hospital admission within 24 hours of the onset of symptoms related to the index event in female and male patients aged ≥ 18 years
- ii) diagnosis of ACS (diagnosis code according to ICD-10 system; I20.0: UAP, I21: acute MI, I22: recurrent MI, I23: complications after acute MI) on the epicrisis (discharge) report form. In addition, the medical records of patients with diagnosis code of I25 (atherosclerotic CV disease) were reviewed to ascertain the presence of clinical signs of ACS. The diagnosis of ACS was verified based on the Universal Criteria for the Definition of Myocardial Infarction [5].

Data collection

The records of a total of 1,000 consecutive patients hospitalised for ACS within the specified study period were reviewed. A case report form was completed for each case, using the information retrieved from the hospital medical records. Patients' most recent medical record information was examined for mortality assessment. Post-discharge medical information of patients with no medical records after hospital discharge or in a 2-year period following hospital discharge was obtained via phone calls. Of the 1,000 patients, 15 were excluded because the diagnosis of ACS was not confirmed, and another 84 were excluded from the 2-year follow-up analysis because they could not be reached despite telephone calls (using the phone number recorded either in the electronic data system or in the patient's medical record) at least in two different days and at different times of the day.

The following information about ACS patients was retrieved from the patients' medical records: demographic characteristics, medical history, CV risk factors, physical examination findings, history of medication (during hospitalisation and recommended for use after hospital discharge), results of laboratory analysis, and in-hospital complications. CV outcomes in the 2-year follow-up period after hospital discharge were also retrospectively retrieved from hospital medical records, the hospital electronic laboratory and clinical recording system, or via phone calls for those with inadequately documented information or no readmission. All data collected were compared between the patients with early ACS and the rest of the study population (old-age group).

Definitions

ACS was divided into UAP (patients without ST-elevation on baseline electrocardiography [ECG], those not developing MI during follow-up, and those with no positive troponin values), STEMI (MI patients with ST-elevation on the baseline ECG and with positive troponin values), and NSTEMI (MI patients without ST-elevation on the baseline ECG and with positive troponin values during the follow-up). Early ACS was defined as age <55 years in men and <60 years in women at the time of the index event.

CV events that occurred during the follow-up period, elective coronary angioplasty, MI, UAP, congestive heart failure, cerebrovascular events and conditions requiring an implantable cardioverter defibrillator and cardiac resynchronization therapy were defined as CV events.

A systolic blood pressure of ≥ 140 mmHg (≥ 130 mmHg for diabetics) and/or a diastolic blood pressure of ≥ 90 mmHg (≥ 80 mmHg for diabetics) were considered high blood pressure (hypertension). Diabetes mellitus was diagnosed if the patient had a diabetes mellitus and had received anti-diabetic treatment and/or had a fasting plasma glucose level of ≥ 126 mg/dL during hospitalisation. CAD was defined as the presence of a previous MI, at least 50% stenosis of a coronary artery on coronary angiogram, coronary angioplasty and/or coronary artery bypass grafting.

A total cholesterol level of ≥ 174 mg/dL was considered a high total cholesterol level, a low-density lipoprotein cholesterol (LDL-C) level of ≥ 100 mg/dL was considered a high LDL-C level, a high-density lipoprotein cholesterol (HDL-C) level of < 40 mg/dL in men and of < 45 mg/dL in women was considered a low HDL-C level. A triglyceride level of ≥ 150 mg/dL was considered a high triglyceride level. Target LDL-cholesterol level with treatment was < 70 mg/dL. Non-HDL-C level was calculated by subtracting the HDL-C level from the total cholesterol level.

The diagnostic scoring for familial hypercholesterolemia (FH) was performed using the Dutch Lipid Clinic Network diagnostic criteria [6–8]. FH scores were calculated according to the definition of De Backer et al [9]. In patients receiving lipid-lowering treatment at the time of hospitalisation, pre-treatment LDL-C level was calculated by multiplying the on-treatment LDL-C level by correction factors defined by Besseling et al. according to the type and dose of the drug used by the patient [10]. According to the total scores, FH was classified as follows: < 3 : unlikely FH, 3-5: possible FH, 6-8: probable FH, and > 8 : definite FH. The presence of xanthomas and corneal arcus could not be evaluated for the diagnosis of FH.

Statistical analysis

Data analyses were performed using Predictive Analytics Software (PASW) version 18.0 (SPSS Inc., Chicago, IL USA for Windows program. Descriptive statistics were expressed as median and 25th percentile (interquartile 1 [Q1]) and 75th percentile (interquartile 3 [Q3]) for numerical variables and as number and percentage for categorical variables. Normality of numerical variables was analyzed by visual (histogram and probability graphics) and analytic methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). For non-normally distributed numerical variables, the comparison of two groups was performed using Mann-Whitney U test. For categorical variables, the chi-square test was used for the comparison of two groups; while Fischer's exact test statistic was used when the chi-square condition was not met. Logistic regression analysis and Cox regression analysis were performed to determine the risk factors for CV events in the follow-up period. The level of statistical significance was accepted as $p < 0.05$.

Results

The median age of the ACS patients, of whom 770 (78.2%) were male, was 60 years (range, 21-93 years). The distribution of ACS patients according to the age group showed that the proportion of patients (29.7%) was highest in the 50-59 age group. There was a significant difference between female and male patients in terms of age distribution ($p < 0.001$). While the proportion of males was higher in the <70-year age group, females were higher in the ≥ 70 -year age group. The distribution of ACS patients according to sex and age groups is shown in **Figure 1**.

Evaluation of the study population in terms of age at the time of the index event showed that 361 (36.6%) of 985 patients met the definition of early CV disease. The general and clinical characteristics of ACS patients according to age at the index event are shown in **Table 1**. The most common index event in the young-age group was STEMI. The proportion of smokers and patients with a body mass index (BMI) of $\geq 30 \text{ kg/m}^2$ was higher in the young group; the presence of hypertension (based on both patient history and blood pressure measurement) and the presence of diabetes mellitus were more common in the old-age group. The proportion of patients having high

total cholesterol, high triglycerides, and/or low HDL-C levels and a family history of CAD were higher in the young-age group.

Evaluation of the study population for the presence of FH revealed that 910 (92.4%) patients had unlikely FH, 68 (6.9%) patients had possible FH, 4 (0.4%) patients had probable FH and 3 (0.3%) patients had definite FH. The total number of patients diagnosed with FH was 75 (7.6%). The presence of FH was significantly higher in the young-age group than in the old-age group (15.5% and 3%, respectively; $p < 0.001$). There were 50 possible (13.9%), 3 probable (0.8%) and 3 definite (0.8%) FH patients in the early ACS group, while there were 18 possible (2.9%), 1 probable (0.2%), and 0 definite (0%) FH in the old-age ACS group.

During the in-hospital period (6.27 ± 4.37 days), 81 patients developed CV complications. There was no significant difference between the young- and old-age groups in the incidence of CV complications. The rates of infections and deaths during hospitalisation were higher in the old-age group (**Table 2**). Of the deaths during the in-hospital period, 33 were due to CV system and one was due to gastrointestinal haemorrhage.

The mean follow-up period after hospital discharge was 30.4 ± 8.4 months for the whole study population. Post-discharge patient in-

Figure 1 | Distribution of acute coronary syndrome patients according to sex and age groups.

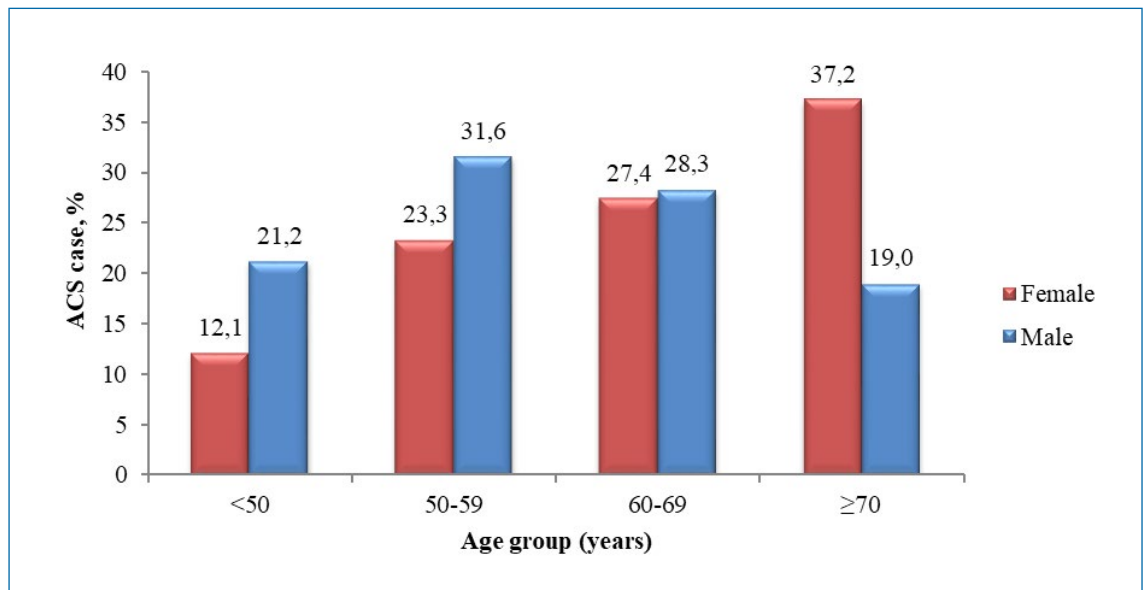


Table 1 | General and clinical characteristics of acute coronary syndrome patients according to the age at index event.

	N	Young-Age Group		Old-Age Group		p
		(Females <60 years old Males <55 years old)	N	(Females ≥ 60 years old Males ≥ 55 years old)		
Age, year	361	49 (45-52)	624	66 (61-74)		<0.001
Sex	361		624			
Female		76 (21.1)		139 (22.3)		0.654
Index event	361		624			
UAS		116 (32.1)		254 (40.7)		
NSTEMI		68 (18.8)		168 (26.9)		<0.001
STEMI		177 (49)		202 (32.4)		

	N	Young-Age Group (Females <60 years old Males <55 years old)	N	Old-Age Group (Females ≥60 years old Males ≥55 years old)	p
Smoking	361		624		
Current		221 (61.2)		214 (34.3)	
Ex-smoker		52 (14.4)		147 (23.6)	<0.001
Never smoked		88 (24.4)		263 (42.1)	
History of obesity	361	152 (42.1)	624	266 (42.6)	0.873
BMI ≥30 kg/m ²	94	28 (29.8)	158	25 (15.8)	0.009
History of hypertension	361	153 (42.4)	624	410 (65.7)	<0.001
Blood pressure ≥140/≥90 mmHg (≥130/≥80 mmHg in diabetics)	360	169 (46.9)	624	345 (55.3)	0.012
Total cholesterol, mg/dL	348	190 (165.5-217)	594	180 (155-213)	0.002
LDL-C, mg/dL	343	112 (91-135)	591	108 (86-133)	0.101
HDL-C, mg/dL	348	38 (33-46)	594	41 (34-49)	0.006
Non-HDL-C, mg/dL	348	151 (120.5-180)	594	139 (113-166)	<0.001
Triglyceride, mg/dL	348	173.5 (120.5-243.5)	594	138 (105-189)	<0.001
History of hyperlipidemia	361	183 (50.7)	624	308 (49.4)	0.687
High total cholesterol level (≥174 mg/dL)	348	233 (67.0)	594	337 (56.7)	0.002
High LDL-C level (≥100 mg/dL)	343	309 (90.1)	591	527 (89.2)	0.659
LDL-C level ≥70 mg/dL (not reaching the treatment goal)	343	225 (65.6)	591	359 (60.7)	0.140
Low HDL-C level (<40 mg/dL in males and <45 mg/dL in females)	348	196 (56.3)	594	283 (47.6)	0.010
High triglyceride level (≥150 mg/dL)	348	210 (60.3)	594	258 (43.4)	<0.001
Presence of diabetes mellitus	361	82 (22.7)	624	197 (31.6)	0.003
Family history of CAD	361	175 (48.5)	624	210 (33.7)	<0.001
Medication (at baseline)					
Statins	361	60 (16.6)	624	120 (19.2)	0.307
Fibrates	361	9 (2.5)	624	7 (1.1)	0.101
Ezetimibe	361	2 (0.6)	624	0 (0)	-
Aspirin	361	103 (28.5)	624	276 (44.2)	<0.001
Clopidogrel	361	22 (6.1)	624	43 (6.9)	0.627
Other anti-platelet agents	361	6 (1.7)	624	6 (1)	0.373
Warfarin	361	5 (1.4)	624	8 (1.3)	1.000
Beta blockers	361	84 (23.3)	622	198 (31.8)	0.004
Calcium channel blockers	361	24 (6.6)	622	92 (14.8)	<0.001
ARB/ACE-I	361	93 (25.8)	624	258 (41.3)	<0.001
Oral antidiabetic agents	361	42 (11.6)	624	117 (18.8)	0.003
Insulin	361	17 (4.7)	624	38 (6.1)	0.363
C-reactive protein level, mg/dL	40	1.24 (0.58-2.47)	45	0.68 (0.18-2.16)	0.096
Thyroid stimulating hormone level, mIU/L	49	1.23 (0.78-2.01)	80	1.28 (0.86-2.62)	0.662

The values are presented as median (Q1-Q3) or number (%), where appropriate.

ARB/ACE-I, angiotensin receptor blocker/angiotensin converting enzyme inhibitor; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low density lipoprotein, UAP: Unstable angina pectoris, NSTEMI: Non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction.

formation was obtained via phone calls in 46.6% of patients, from hospital medical records in 18.8% of patients, and by both in 34.6% of the patients. During the follow-up period, 50.6% of the patients experienced CV events and 8.1% (n=70) died. The cause of death was CV events in 51 patients; other causes of death included malignancy (n=10), renal failure (n=5), infections (n=3) and chronic obstructive pulmonary disease (n=1). The rates of CV events and death during the follow-up period were significantly higher in the old-age group (Table 2).

To determine the factors affecting the development of CV events during the follow-up period, a logistic regression analysis was performed by creating a model that included the variables of index event, age, hyperlipidaemia, hypertension, previous use of fibrates

and previous use of beta blockers. Accordingly, the index event (STEMI or NSTEMI) and the presence of hypertension were found to be significant increasing risk factors. Being in the young-age group was a significant decreasing factor (Table 3). Cox regression analysis was performed to determine the factors affecting mortality during the follow-up period by creating a model including the following parameters: sex, age group, smoking, obesity, hypertension, diabetes mellitus, family history, use of angiotensin receptor blocker/angiotensin-converting enzyme inhibitor (ACE/ARB), use of insulin, in-hospital CV complications, hospital infections, LDL-C levels <70 mg/dL, non-HDL-C levels <130 mg/dL, and triglyceride levels \geq 150 mg/dL. The significant associated factors for mortality were female sex, advanced age, in-hospital CV complications (Table 4).

Table 2 | In-hospital and post-discharge (follow-up) events according to the age.

	N	Young-Age Group (Females <60 years old Males <55 years old)	N	Old-Age Group (Females \geq 60 years old Males \geq 55 years old)	p
<i>In-hospital</i>					
Cardiovascular complications	327	24 (7.3)	574	57 (9.9)	0.191
Infection	327	11 (3.4)	574	37 (6.4)	0.048
Death	327	5 (1.5)	574	29 (5.1)	0.008
<i>Follow-up</i>					
Cardiovascular events	322	148 (46.0)	545	291 (53.4)	0.034
Death	322	13 (4.0)	545	57 (10.5)	0.001

Table 3 | Factors affecting the development of cardiovascular events during the follow-up period

	p	OR	95% CI
Index event (unstable angina pectoris) (Reference)	<0.001		
NSTEMI	0.001	1.858	1.30-2.65
STEMI	<0.001	2.349	1.71-3.23
Young age*	0.006	0.669	0.50-0.89
Presence of hypertension**	0.047	1.320	1.00-1.74

*<55 years in men and <60 years in women; **Blood pressure \geq 140/ \geq 90 mmHg (\geq 130/ \geq 80 mmHg in diabetics).

CI, confidence interval; OR; Odds ratio; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction.

Table 4 | Factors affecting mortality during the follow-up period.

	p	OR	95% CI
Sex (Female)	0.014	3.061	1.25-7.48
Age group (<50 years) (Reference)	<0.001		
50-59 years	0.372	1.612	0.57-4.60
60-69 years	0.036	2.895	1.07-7.81
\geq 70 years	<0.001	6.452	2.45-17.01
Presence of obesity	0.051	1.606	1.00-2.59
Presence of hypertension	0.054	0.410	0.17-1.01
Presence of in-hospital cardiovascular complications	0.042	2.264	1.03-4.97
Presence of hypertension*Sex	0.028	3.359	1.14-9.92

CI, confidence interval; OR; Odds ratio.

Discussion

To the best of our knowledge, this retrospective cohort of 985 patients with ACS is the first study reporting the incidence of early ACS (36.6%) in Turkish patients. There are 3 large ACS registries in Turkey; the TUMAR study, the TURKMI study, and the Turkish arm of the EPICOR study [11–13]. The TUMAR registry enrolled 3,358 patients with a diagnosis of acute MI within 24 hours of symptom onset in the early years of 2000s. The Turkish arm of the EPICOR study, conducted in 2010 and 2011, reported data on 1,034 patients hospitalised for ACS within 24 hours of symptom onset who had a final diagnosis of UA, STEMI or NSTEMI and survived to discharge from 34 centers in Turkey [11]. TURKMI is a nationwide registry that was conducted to highlight the characteristics of patients admitted with acute MI within 48 hours of the onset of symptoms to the selected cardiology centers capable of PCI in Turkey [13]. The TURKMI study observed a 22.1% of early MI prevalence defined as < 50 years of age among patients with STEMI. The TUMAR study reported a 72% frequency of patients with early MI (defined as < 65 years of age with no sex criteria) and no further information was available on the clinical or laboratory data of the TUMAR population with early MI. The EPICOR study also did not provide information on the frequency and the clinical characteristics of patients with early ACS [11]. The only information on the frequency of early ACS for this population could be obtained from the EUROASPIRE studies, conducted in European countries, including Turkey. The incidence of young MI defined as an index event under the age of 50 years was overall 12% in the European countries as a whole, while it was 19% in the Turkish arm of the EUROASPIRE IV (78 centers from 24 countries) [4]. Moreover, the mean age of the study population was 64.0±9.6 years (with the lowest in Turkey [58.7±10.1 years] and the highest in Germany [67.4±8.9 years]). The mean age of the ACS patients in the TUMAR and EPICOR registries was 58±12 and 61.8±12 years, respectively. In the EUROASPIRE III study, the median age of CAD patients in Turkey was 60.5 years [14]. Likewise, in the present study, the median age of ACS patients was 60 years. All these data may suggest that people in Turkey suffer from coronary events at a younger age. This high rate of premature CV disease might be due to the overall high consanguinity rate (23.3%), which leads to increased genetic lipid and/or hereditary thrombotic disorders in Turkey [2,14].

In the present study, the most common index event in the young-age group was STEMI, whereas it was UAP in the old-age group. The proportion of smokers and those with a BMI ≥30 kg/m² was higher in the young-age group. However, hypertension (based on both history and blood pressure measurement) and diabetes mellitus were more commonly observed in the old-age group. A study from Japan reported similar results; 24.2% of 6,255 ACS patients were aged <60 years [15]. In this study, traditional CV risk factors such as history of MI, heart failure, diabetes mellitus, chronic kidney disease and hypertension were more prevalent among patients aged >60 years, whereas dyslipidemia, smoking and a family history of CAD were more prevalent among patients aged <60 years [15,16]. In a study from New Zealand, in which 1,199 patients presenting with MI were evaluated, 12.8% of patients were in the young-age group [16]. In this study, the rates of males, higher BMI, family history of premature CAD, and current smokers were reported to be higher in the young-age group than in the older age group. However, hypertension, dyslipidaemia and diabetes were observed less frequently in the young-age group.

Acute coronary syndromes occur approximately 10 years later in women than in men [17]. Hence, it has been reported that female ACS patients are generally older than male patients [17–20]. In a study from France, a 6.3% increase in ACS-related hospital visits was

observed in women aged <65 years over a 10-year period [21]. In the present study, distribution of age according to sex in ACS patients revealed that the rate of men was higher in young ages (<60 years), whereas the rate of women was higher in older ages (≥70 years), as expected.

Another important finding of this study is the higher prevalence of FH among young ACS patients. FH is an underdiagnosed condition that causes an increased risk of early CAD, and its prevalence in the general population has been reported to range from 0.01% to 0.58% [22,23]. The prevalence of FH among CAD patients has been reported to be higher, with a prevalence of potential FH (FH score ≥6) of 3.7%–8.3% [9,24]. The prevalence of FH has been reported to be 10-fold higher in patients hospitalised for ACS than in the general population [25]. The prevalence of FH in early ACS varies depending mainly on the cut-off age used for the definition of early onset; the lower the cut-off age, the higher the FH prevalence [2,25–32]. In the present study, FH prevalence was significantly higher in the young-age group than in old-age group (15.5% versus 3%). Our data are the first report of FH prevalence in an early ACS population from Turkey. In the Danish population, the prevalence of FH (probable+definite) is 6.9% among patients with premature MI (defined as MI before the age of 60 years) [29]. Another ACS cohort from Switzerland has shown a 4.8% prevalence of FH in patients with premature ACS [25,27]. In the present study, the rate of patients diagnosed with FH (possible+probable+definite) in ACS patients is 7.6%. The discrepancy between these early ACS/MI populations could also be due to inclusion criteria other than the defined age, i.e. in the EUROASPIRE IV study, as the patients were not enrolled consequently, a selection bias could exist [9].

The in-hospital mortality rate for ACS patients exceeds 5% [20]. In a large-scale study from China, the in-hospital mortality rate for ACS patients in two different hospitals was 2.5% and 3.6% [33]. A study from Japan reported higher mortality rates in older ACS patients (2.4% in those aged <60 years and 4.9% in those aged >60 years) [15]. In the present study, the in-hospital mortality rate was 3.8%, with higher rates in the older-age group than in the young-age group (5.1% vs. 1.5%).

In the present study, the frequency of CV events during a mean follow-up period of 30.4±8.4 months was 50.6% in patients discharged from hospital, while the mortality rate during the same period was 8.1%. The rates of CV events and death were higher in the old-age group than in the young-age group. During the follow-up period, the significant risk factors for CV events were the index event (STEMI or NSTEMI), the presence of hypertension and being in the young-age group was a negative risk factor. Moreover, the significant risk factors associated with mortality during the follow-up period were female sex, old age, and in-hospital CV complication.

Limitations of the Study

The retrospective nature of the study could be considered a limitation. However, retrospective data collection is valuable as it reflects the real-life setting. Nevertheless, physical signs of FH (xanthelasmas and xanthomas) and a detailed family history of high cholesterol levels and premature CAD, which are among the important diagnostic criteria of FH, could not be evaluated because of the retrospective design of this study. Therefore, the true prevalence of FH is likely underestimated. However, most of the previous studies harbor this limitation. On the other hand, the EUROASPIRE IV study, which demonstrated the prevalence of FH in ACS patients, was also a retrospective study in which the prevalence of FH was calculated using the same methodology as in the present study ([4,9]3,9). However,

in EUROASPIRE IV, patients were invited to participate in a face-to-face interview, which could also help to obtain more information on family history, etc. The lack of genetic analysis for the diagnosis of FH could also be regarded as a limitation.

Conclusion

In this retrospective ACS cohort from a single center in Turkey, a very high rate (36.6%) of early ACS was observed. Compared to older patients, young ACS patients were more likely to be smokers, more obese, less diabetic and less hypertensive. High total cholesterol levels, high triglyceride levels, high non-HDL cholesterol levels, low HDL-cholesterol levels, a family history of CAD and FH were also more frequently observed in the young ACS group. Both in-hospital and 2-year follow-up mortality rates were significantly lower in the old-age group.

References

- [1] Kayikcioglu M, Tetik Vardarli A. How to Generate Unbiased Data in Molecular Genetic Studies in Patients with Early Onset Coronary Artery Disease or Premature Myocardial Infarction? *Turk Kardiyol Dern Arsivi-Archives Turkish Soc Cardiol.* 2022 Sep 2;50(6):404-6.
- [2] Kayikcioglu M, Ozkan HS, Yagmur B. Premature Myocardial Infarction: A Rising Threat. *Balkan Med J.* 2022;39(2):83-95.
- [3] Rallidis LS, Kosmas N, Tsirebolos G, Rallidi M, Kiouri E, Kalpakos D. Prevalence of heterozygous familial hypercholesterolemia and combined hyperlipidemia phenotype in very young survivors of myocardial infarction and their association with the severity of atheromatous burden. *J Clin Lipidol.* 2019 May;13(3):502-8.
- [4] Tokgozoglul L. EUROASPIRE-IV: Study of the European Society of Cardiology on Lifestyle, Risk Factors, and Treatment Approaches in Patients with Coronary Artery Disease: Data from Turkey. *Turk Kardiyol Dern Arsivi-Archives Turkish Soc Cardiol.* 2016.
- [5] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation.* 2018 Nov 13;138(20).
- [6] Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *Am J Epidemiol.* 2004 Sep 1;160(5):407-20.
- [7] Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. *Curr Opin Lipidol.* 2012 Aug;23(4):282-9.
- [8] Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: Consensus Statement of the European Atherosclerosis Society. *Eur Heart J.* 2013 Dec 1;34(45):3478-90.
- [9] De Backer G, Besseling J, Chapman J, Hovingh GK, Kastelein JJP, Kotseva K, et al. Prevalence and management of familial hypercholesterolemia in coronary patients: An analysis of EUROASPIRE IV, a study of the European Society of Cardiology. *Atherosclerosis.* 2015 Jul;241(1):169-75.
- [10] Besseling J, Kindt I, Hof M, Kastelein JJP, Hutten BA, Hovingh GK. Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. *Atherosclerosis.* 2014 Mar;233(1):219-23.
- [11] Ertaş FS, Tokgözoğlu L, EPICOR Study Group. Pre- and in-hospital antithrombotic management patterns and in-hospital outcomes in patients with acute coronary syndrome: data from the Turkish arm of the EPICOR study. *Anatol J Cardiol.* 2016 Dec;16(12):900-15.
- [12] Enar R. TUMAR Akut Miyokard İnfarktüsü. 1st ed. Istanbul; 2004.
- [13] Erol MK, Kayikcioglu M, Kılıçkap M, Arın CB, Kurt İH, Aktaş İ, et al. Baseline clinical characteristics and patient profile of the TURKMI registry: Results of a nation-wide acute myocardial infarction registry in Turkey. *Anatol J Cardiol.* 2020;24(1):43-53.
- [14] Tokgözoğlu L, Kaya EB, Erol Ç, Ergene O, Aydoğdu S, Tekin M, et al. EUROASPIRE III: A comparison between Turkey and Europe | EUROASPIRE III: Türkiye ile Avrupa'nın karşılaştırılması. *Turk Kardiyol Dern Ars.* 2010;38(3).
- [15] Hirota Y, Sawano M, Numasawa Y, Ueda I, Noma S, Suzuki M, et al. Characteristics and in-hospital outcomes in young patients presenting with acute coronary syndrome treated by percutaneous coronary intervention. *Cardiovasc Interv Ther.* 2018 Apr 5;33(2):154-62.
- [16] Matsis K, Holley A, Al-Sinan A, Matsis P, Larsen PD, Harding SA. Differing Clinical Characteristics Between Young and Older Patients Presenting with Myocardial Infarction. *Heart Lung Circ.* 2017 Jun;26(6):566-71.
- [17] Kawamoto KR, Davis MB, Duvernoy CS. Acute Coronary Syndromes: Differences in Men and Women. *Curr Atheroscler Rep.* 2016 Dec;18(12):73.
- [18] Erol MK, Kayikcioglu M, Kılıçkap M. Rationale and design of the Turkish acute myocardial infarction registry: The Turkmi study. *Anatol J Cardiol.* 2020;23(3):169-75.
- [19] Kılıçkap M, Erol MK, Kayikcioglu M, Kocayigit I, Gitmez M, Can V, et al. Short and Midterm Outcomes in Patients With Acute Myocardial Infarction: Results of the Nationwide TURKMI Registry. *Angiology.* 2021;72(4):339-47.
- [20] Chan MY, Du X, Eccleston D, Ma C, Mohanan PP, Ogita M, et al. Acute coronary syndrome in the Asia-Pacific region. *Int J Cardiol.* 2016 Jan 1;202:861-9.
- [21] Gabet A, Danchin N, Juillière Y, Olié V. Acute coronary syndrome in women: rising hospitalizations in middle-aged French women, 2004-14. *Eur Heart J.* 2017 Apr 7;38(14):1060-5.
- [22] Casula M, Catapano AL, Rossi Bernardi L, Visconti M, Aronica A. Detection of familial hypercholesterolemia in patients from a general practice database. *Atheroscler Suppl.* 2017 Oct;29:25-30.
- [23] Zamora A, Masana L, Comas-Cufí M, Vila À, Plana N, García-Gil M, et al. Familial hypercholesterolemia in a European Mediterranean population-Prevalence and clinical data from 2.5 million primary care patients. *J Clin Lipidol.* 2017;11(4):1013-22.
- [24] Faggiano P, Pirillo A, Griffo R, Ambrosetti M, Pedretti R, Scorcù G, et al. Prevalence and management of familial hypercholesterolemia in patients with coronary artery disease: The heredity survey. *Int J Cardiol.* 2018 Feb 1;252:193-8.
- [25] Gencer B, Nanchen D. Identifying familial hypercholesterolemia in acute coronary syndrome. *Curr Opin Lipidol.* 2016 Aug;27(4):375-81.
- [26] Kayikcioglu M, Uzun HG, Vardarli AT, Tokgözoğlu L. Monozygotic twins with familial hypercholesterolemia and high lipoprotein(a) levels leading to identical cardiovascular outcomes: Case report and review of the literature. *Turk Kardiyol Dern Ars.* 2020;48(5):531-8.
- [27] Nanchen D, Gencer B, Muller O, Auer R, Aghlmandi S, Heg D, et al. Prognosis of Patients With Familial Hypercholesterolemia After Acute Coronary Syndromes. *Circulation.* 2016 Sep 6;134(10):698-709.

- [28] Li S, Zhang Y, Zhu CG, Guo YL, Wu NQ, Gao Y, et al. Identification of familial hypercholesterolemia in patients with myocardial infarction: A Chinese cohort study. *J Clin Lipidol*. 2016;10(6):1344-52.
- [29] Mortensen MB, Kulenovic I, Klausen IC, Falk E. Familial hypercholesterolemia among unselected contemporary patients presenting with first myocardial infarction: Prevalence, risk factor burden, and impact on age at presentation. *J Clin Lipidol*. 2016;10(5):1145-1152.e1.
- [30] Pang J, Poulter EB, Bell DA, Bates TR, Jefferson VL, Hillis GS, et al. Frequency of familial hypercholesterolemia in patients with early-onset coronary artery disease admitted to a coronary care unit. *J Clin Lipidol*. 2015;9(5):703-8.
- [31] Koivisto UM, Hämäläinen L, Taskinen MR, Kettunen K, Kontula K. Prevalence of familial hypercholesterolemia among young north Karelian patients with coronary heart disease: a study based on diagnosis by polymerase chain reaction. *J Lipid Res*. 1993 Feb;34(2):269-77.
- [32] Brønne I, Kleinecke M, Reiz B, Graf E, Strom T, Wieland T, et al. Systematic analysis of variants related to familial hypercholesterolemia in families with premature myocardial infarction. *Eur J Hum Genet*. 2016 Feb;24(2):191-7.
- [33] Peng Y, Du X, Rogers KD, Wu Y, Gao R, Patel A, et al. Predicting In-Hospital Mortality in Patients With Acute Coronary Syndrome in China. *Am J Cardiol*. 2017 Oct 1; 120(7):1077-83.