Original Research

Epidemiological Characteristics and In-Hospital Management of Acute Coronary Syndrome Patients in Greece: Results from the TARGET Study

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Introduction: Conduction of national surveys is needed to depict temporal trends in the risk profile, type of implemented treatment strategy and outcome of patients with acute coronary syndromes (ACS). The TARGET study is a multicenter, observational study that aimed to evaluate the epidemiological characteristics, management pattern and outcome of ACS patients in Greece.
Methods: A total of 418 consecutive patients with ACS (44.7% STEMI, 34.2% NSTEMI, 21.1% unstable angina) from 17 centers (52.9% with catheterization facilities) were enrolled in the study (78.0% males, 63.9 ± 12.9 years).
Results: Overall, 67.9% of the patients had hypertension, 27.5% were diabetics and 57.4% had dyslipidemia. Thrombolytic therapy (60.7% tenecteplase, 38.2% reteplase) was administered in 22.7% of the study population, while invasive management was performed in 40.2% of patients (27.0% PCI and 1.0% CABG) during the index hospitalization. In-hospital all-cause mortality was 1.9%, with 12.2% of patients experiencing adverse clinical events. Evidence-based medications were prescribed to the majority of enrolled patients during hospitalization and upon discharge (97% and 94% received aspirin, 93% and 84% clopidogrel, 87% and 86% beta-blockers, 96% and 93% statins, respectively).
Conclusion: The prevalence of modifiable risk factors exhibits an increasing trend among ACS patients in Greece. The prescription pattern of evidence-based medications has improved considerably, while there remains considerable room for improvement in expanding the implementation of invasive management in real-world clinical practice.

Acute coronary syndromes (ACS) constitute a major cause of morbidity and mortality worldwide. Non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA) account for about 2.5 million hospital admissions annually worldwide, while ST elevation myocardial infarction (STEMI) accounts for another 1 million.[1] The incidence of ACS varies greatly among different European countries, partly due to disparities in dietary habits and the prev-

alence of cardiovascular risk factors.[2] Furthermore, the management and outcome of ACS patients is highly dependent on the implementation rate of mortality-reducing therapies as well as the organization of the healthcare infrastructure to enable early patient management and timely reperfusion of the myocardium at risk.

It is generally accepted that there is a great need for national surveys that can shed light on the epidemiology, treatment and prognosis of the everyday patient population. This type of epidemiological study overcomes the main limitation of randomized clinical trials, namely the highly controlled clinical setting that impairs the pragmatic assessment of the characteristics, management and outcome of real-world patients.[3-5] Five years after the completion of the HELIOS study, a nationwide survey that enrolled patients with acute myocardial infarction,[6] we conducted the TARGET study, a multicenter, 2-phase, nationwide, observational study, that aims to provide further data concerning the epidemiological profile, management pattern and outcome of ACS patients in Greece.

Methods

Study design

The TARGET study is an observational study with two phases: one cross-sectional phase covering the index event information (TARGET Baseline) and one prospective phase covering a six-month period after the index event (TARGET Cohort). Data from TARGET Baseline are reported here. The study was designed to enroll consecutive patients admitted to 17 participating centers in Greece, with an index diagnosis of ACS (STEMI, NSTEMI or UA). Case definition was standardized based on the relevant guidelines.[7] The participating hospitals were selected on the basis of encompassing the full spectrum of hospitals that admit patients with ACS in Greece (public and private, academic and non-academic, rural and urban hospitals, with and without catheterization facilities) in order to increase the external validity of the study results. All patients were informed about the study and signed the informed consent form.

Data were selected on patients' socio-demographic and anthropometric characteristics (age, height, weight, waist circumference, body mass index [BMI], race, marital status, educational level, employment status), their past dietary habits and physical activity level. All patients were asked about their past medical car-

diovascular (established coronary artery, cerebrovascular, or peripheral arterial disease, abdominal aortic aneurysm, heart failure) and non-cardiovascular history and the prevalence of the following coronary risk factors: diabetes mellitus, smoking status, hypertension (blood pressure over 140/90 mmHg, or treatment with antihypertensive agents), dyslipidemia (total cholesterol over 190 mg/dL or treatment with hypolipidemic agents), family history of premature coronary artery disease. Information was also collected about the type of clinical presentation and time of symptom onset, the selected means and duration of transportation to the index hospital, the type of medication used before admission, and patients' vital signs in the emergency department (heart rate, respiration rate, systolic and diastolic blood pressure and body temperature).

The case report form also included information about the index 12-lead ECG (magnitude of ST elevation or depression, presence of T-wave inversion or acute atrioventricular conduction disorders), patient's lipid profile within 24 hours from admission (total, high-density lipoprotein [HDL] and low-density lipoprotein [LDL] cholesterol; triglycerides; apolipoprotein AI, B) biomarkers (troponin I and T, CK-MB, high sensitivity C-reactive protein [CRP], brain natriuretic peptide [BNP], N-terminal pro BNP [NT-proBNP], fibrinogen, if applicable), serum creatinine and blood glucose levels.

Risk stratification using the Framingham Risk Score (FRS) and the SCORE risk prediction model was applied in patients who did not have coronary artery disease (CAD) or its risk equivalents, in order to estimate the 10-year risk of a coronary heart disease event or cardiovascular death, respectively.[8,9] For the purposes of this study, the SCORE model version for Greece was used. Furthermore, based on the recent ESC recommendations on myocardial revascularization, we calculated the GRACE risk score for risk stratification of patients upon admission.[10]

Data were also recorded on the therapeutic strategy followed (invasive versus noninvasive management), the type of other noninvasive examinations performed during hospitalization, discharge diagnosis, occurrence of clinical events during hospitalization, type of medications recommended, and instructions on lifestyle changes given upon patient discharge.

Statistics

Sample size calculation was based on the confidence limit approach rather than test power considerations, aiming to ensure adequate precision estimates. Based

on this rationale, 385 patients were required to achieve a ±5% precision of estimates, given that the expected percentage of the primary study endpoint (percentage of patients within LDL-C target upon hospital admission) was 50%. Assuming a percentage of 8% of non-evaluable subjects, the estimated size of the study population was 418 patients.

Descriptive statistical analysis was applied to all the study's cross-sectional data. All categorical variables are expressed in counts (N) and percentages (%). Continuous variables are summarized with the use of descriptive statistical measures. The normality of distribution of continuous variables was examined using the Kolmogorov-Smirnov test in order to determine whether or not to use parametric methods for the analysis of the sample data. All the aforementioned statistical tests were two-sided and performed at a 0.05 significance level. Missing data were replaced. No inferential statistics were used, as all study objectives pertained to quantitative descriptions. Data processing and analysis were performed using the statistical package SPSS v. 17.0.

Results

Demographic characteristics and past medical history

In total, 418 patients from 17 participating centers were enrolled in the study. Among 17 participating centers, 7 were located within Attica, enrolling 49.3% of the total population, 9 had catheterization facilities, including 49.5% of the sample population, and 11 hospitals were public (Figure 1). The majority of the enrolled patients were males, with a male-to-female ratio of 3.5 (males/females: 78.0%/22.0%). The mean age of the study population was 63.9 ± 12.9 years, the mean height 169.3 ± 8.4 cm, the mean weight 82.6 ± 16.5 kg, and the mean BMI was 28.8 ± 4.8 kg/m^2.

Regarding patients' physical activity and dietary pattern prior to the index event, 61.2% of the study participants used to follow a diet of low nutritional value, while 55.7% of them had adopted a sedentary lifestyle with a lack of physical activity. Baseline data regarding patients' past history of CAD, CAD equivalents, as well as coronary risk factors are presented in Table 1.

Outside Attica	
General Hospital Chalkida	36
Chios General Hospital Skylitsion	29
General Hospital of Volos	29
University Hospital of Heraklion	21
University Hospital of Larissa	21
General Hospital of Komotini	18
General Hospital of Chania	18
Bodosakeio Hospital of Ptolemaida	17
General Hospital of Edessa	15
University Hospital of Ioannina	8
Inside Attica	
General Hospital Agia Varvara	42
Thriassio General Hospital, Elefsina	41
University Hospital Attikou	37
Sismanoglio General Hospital	36
Euroclinic Hospital	29
Hygeia Hospital	17
Henry Dunant Hospital	4
Total	**418**

Figure 1. Geographical distribution and list of participating centers with the respective numbers of enrolled patients.

Table 1. Baseline prevalence of coronary risk factors, past history of coronary artery disease or coronary artery disease risk equivalents.

	n	%
Smoking status		
No smoker	109	26.1
Previous smoker	111	26.6
Occasional smoker	3	0.7
Current smoker	195	46.7
If current smoker: pack-years		
mean ± SD	50.6 ± 33.3	
Hypertension	284	67.9
Dyslipidemia	240	57.4
Diabetes mellitus	115	27.5
Type I	8	1.9
Type II	107	25.6
Family history of premature CAD	124	29.7
Coronary artery disease	129	30.9
Stable angina	18	4.3
Unstable angina	15	3.6
AMI	71	17.0
PCI	58	13.9
CABG	26	6.2
Cerebrovascular disease	44	10.5
Stroke	29	6.9
Ischemic	24	5.7
Hemorrhagic	2	0.5
Unspecified	3	0.7
Transient ischemic attack	23	5.5
> 50% carotid artery stenosis	14	3.3
Peripheral arterial disease	33	7.9
Abdominal aortic aneurysm	7	1.7

AMI – acute myocardial infarction; CABG – coronary artery bypass grafting; CAD – coronary artery disease; PCI – percutaneous coronary intervention.

Table 2. Percentage of patients within LDL-C goal levels among different LDL-C target categories based on the updated NCEP-ATP III recommendations.

LDL-C target category	Study population on LDL-C target upon hospital admission, N (%)		p
	Yes (n=107)	No (n=282)	
<70 (n=136/144*)	22 (16.2)	114 (83.8)	
<100 (n=143/154†)	34 (23.8)	109 (76.2)	
<130 (n=99/99)	42 (42.4)	57 (57.6)	0.0001‡
<160 (n=11/11)	9 (81.8)	2 (18.2)	
Total	107 (27.5)	282 (72.5)	

*In 8 patients the LDL-C value was missing. †In 11 patients LDL-C value was missing. ‡Statistically significant as assessed by chi-square test.

Baseline lipid parameters and risk score

Overall, 72.5% of the total patient population had baseline LDL-C levels above the respective recommended goal according to the 2004-updated National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) guidelines.[11] In particular, 83.8% and 76.2% of the patients belonging to LDL-C target categories of <70 mg/dL and <100 mg/dL, were above the respective target LDL-C levels at admission. No significant difference in the percentage of patients within LDL-C goal levels was found among the patient subgroups with different index ACS diagnosis (28.4% of STEMI patients, compared to 27.3% for NSTEMI and 25.9% for UA patients). There was a statistically significant difference in the percentage of patients within LDL-C target levels at admission among patient subgroups belonging in different LDL-C target categories (p<0.0001; Table 2).

In the subgroup of ACS patients without prior CAD or CAD risk equivalents (N=203, 48.6% of the total study population), 27.0% were considered to be of low risk, 41.3% of intermediate risk and only 31.8% were classified in the high or very high risk category based on the Framingham point score system. Based on the Heart Score risk prediction model, only 27.4% of enrolled ACS patients without prior CAD were identified to be at very high risk, 33.7% were classified as high risk and 38.9% were categorized as low risk (SCORE <5%). The classification of patients into different risk categories based on the calculation of the GRACE risk score is presented in Figure 2.

Diagnosis, management and outcome

A diagnosis of STEMI was documented in 44.7% of the enrolled patients, NSTEMI in 34.2% and UA in 21.1%. In 61.7% of cases, patients reached hospital care by self-transportation, while 33.5% of patients were taken to hospital by ambulance. The mean waiting period from ambulance call was 20 ± 16.5 min, while the mean duration of transportation to the index hospital, irrespective of the mode of transport, was 34.1 ± 46.4 min. The median "pain-to-door" time was 180 minutes (25th and 75th percentiles were 90 min and 552 min, respectively) and was similar among hospitals within and outside Attica.

In total, 22.7% of the study population received thrombolytic therapy (60.7% tenecteplase, 38.2% reteplase). Invasive management of the index event was performed in 40.2% of patients, with 27.0% undergoing percutaneous coronary intervention (PCI) and 1.0% coronary artery bypass grafting (CABG) during the index hospitalization. In the subgroup of pa-
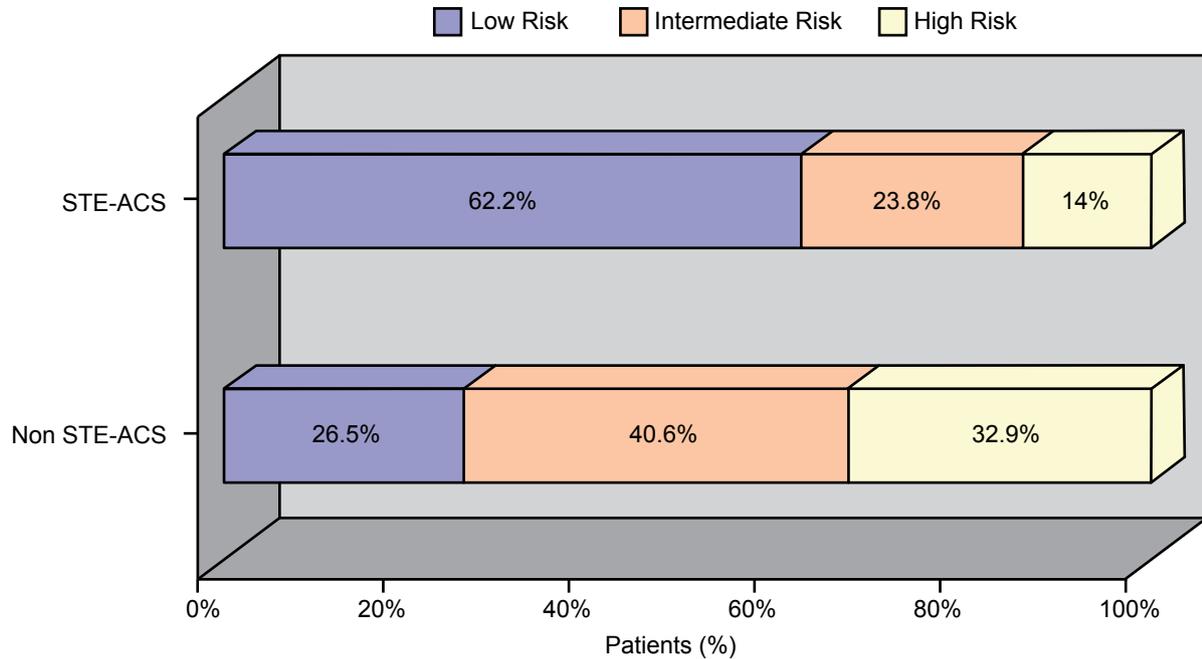
Figure 2. Risk stratification of patients for in-hospital mortality based on the calculation of the GRACE risk score. STE – ST-elevation; ACS – acute coronary syndrome.

tients admitted to hospitals with catheterization facilities (n=207), 80.2% were managed invasively, while 54.1% and 1.9% underwent PCI and CABG, respectively. Prior pharmacological management based on patients' self-reporting, as well as medications administered during hospitalization and upon discharge, are presented in Figure 3.

The mean length of hospitalization was 7.1 ± 4.6

days. In total, 12.2% of patients (51/418) experienced at least one adverse clinical event during hospitalization (Figure 4). Twelve patients (2.9%) experienced a major cardiovascular event (cardiovascular death, myocardial infarction or stroke) during hospitalization. In-hospital all-cause mortality was 1.9% (8 out of 418 patients), while cardiovascular mortality rate was 1.7% (7 out of 418 patients).
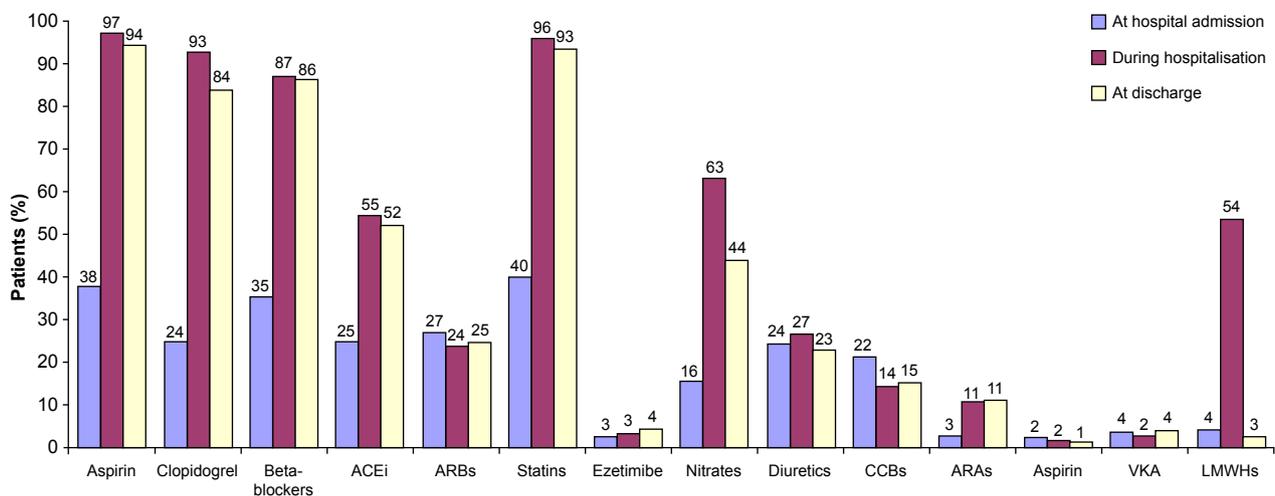

Figure 3. Prior pharmacological management based on patients' self reporting (blue bars), medications administered during in-hospital management (red bars), and at patient discharge (white bars). ACEi – angiotensin converting enzyme inhibitors; ARBs – angiotensin receptor blockers; CCBs – calcium channel blockers; ARAs – aldosterone receptor antagonists; VKA – vitamin K antagonists; LMWHs – low molecular weight heparins.
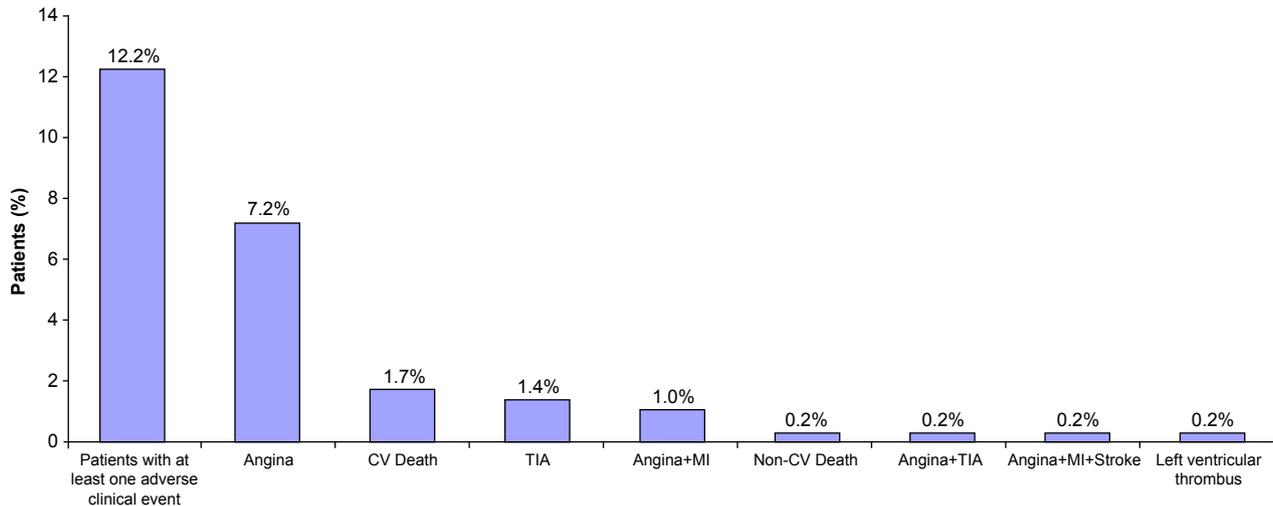
Figure 4. Distribution of patients experiencing different types of adverse clinical events during hospitalization. CV – cardiovascular; TIA – transient ischemic attack; MI – myocardial infarction.

Discussion

The epidemiological characteristics of ACS patients and the pattern of their management change over time, mainly because of temporal trends in the prevalence of coronary risk factors, differences in the availability of healthcare resources and facilities, adoption of contemporary adjunctive pharmacology and revascularization strategies, and the varying degree of implementation of treatment guidelines. In this context, repeated surveys are needed to account for the dynamic nature of the abovementioned variables and to provide relevant, comprehensive and updated information. Five years after the completion of the countrywide HELIOS registry,[6] which included patients with acute myocardial infarction, we conducted the TARGET study, a multicenter, nationwide survey, designed to provide data regarding the epidemiological characteristics, the "real-world" management and the outcome of patients with ACS in Greece.

A well-acknowledged methodological challenge of similar registries is the representativeness of the sample population and the accurate reflection of the existing diversity in the everyday management of ACS patients. In an attempt to address this issue, centers from different prefectures were selected to participate in the present study, encompassing the whole spectrum of hospitals that admit ACS patients, maintaining a balanced ratio of university hospitals and hospitals with catheterization facilities. Furthermore, in order to avoid systematic bias in patient enrollment, investigators were requested to include consecutive patients admitted with an index diagnosis of ACS, with consistency in case definition. Periodic monitoring visits were conducted to all study sites in order to ensure the quality of reported data.

In our ACS population, 68% of patients were hypertensive and 57% had dyslipidemia. These findings denote an increasing trend in the prevalence of hypertension and dyslipidemia among ACS patients, since the respective rates were 45% and 35% in surveys conducted in 1990s, and 59% and 50% in the HELIOS study, respectively.[6,12,13] The increase in the prevalence of hypertension in the TARGET compared to the HELIOS population is even more pronounced if we take into account the lower average age of the TARGET patient population (63.9 years versus 68 years). In addition, in comparison to the HELIOS study, the prevalence of diabetes in our patient population was slightly lower (27.5% versus 31%), while the percentage of current or ex-smokers was rather similar (71% versus 73.9%). Interestingly, upon admission, almost three quarters of the patient population had LDL-C levels above the respective recommended goal according to the 2004-updated NCEP-ATPIII guidelines. The continuing high prevalence of modifiable risk factors among ACS patients is at least partly associated with the adoption of adverse lifestyle trends, such as unhealthy dietary habits, lack of exercise and smoking, and stresses the need for the effective implementation of preventive strategies by all healthcare professionals in everyday clinical practice.

In the subgroup of ACS patients who did not have prior CAD or CAD risk equivalents we retrospectively applied the FRS and the SCORE risk prediction models to evaluate the baseline risk status. Interestingly, only 31.8% and 27.4% of those patients were actually categorized in the high or very high risk category based on the FRS and SCORE model, while 38.9% and 27% of them were classified in the low risk category, respectively. These results are obviously not adequate to evaluate the performance of these risk prediction systems with a long latent period between risk assessment and disease development, particularly for the SCORE system which actually predicts the risk only of fatal cardiovascular events. However, this apparent discrepancy seems to reflect the inherently limited ability of these score systems to account for the residual coronary risk, which is not attributed to the risk factors incorporated in these prediction models. Indeed, several studies have shown that asymptomatic individuals categorized as low risk by FRS have significant subclinical coronary atherosclerosis.[14,15]

We also sought to investigate the parameters that influenced pre-hospital delay in patients with ACS in a "real-world" setting. It is worth noting that, despite the fact that the percentage of patients that came to hospital by ambulance was practically double in comparison to the HELIOS study, the median delay between symptom onset and arrival at the hospital was identical. Although there is always room for improvement in arrival delays and transport times performed by the emergency medical services, the factor that has the major impact on the long treatment delay is patient delay in seeking medical care. Therefore, mass media interventions and public educational campaigns are needed to enhance public awareness of warning symptoms and signs of heart attack, especially among lower-income and lower-education citizens.

The TARGET study also shed light on the management pattern of ACS patients, assessing the rate of use of adjunctive medical treatment and the rate of implementation of invasive treatment in everyday practice in Greece. It should be pointed out that in our survey we found an increased rate of use of all types of evidence-based medications as compared to the HELIOS study. Furthermore, upon discharge, a greater proportion of our patients were prescribed aspirin, thienopyridines, b-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins in comparison to the respective ratios reported in the HELIOS study, as well as the second Euro Heart Survey on ACS.[6,16] These results are highly encouraging, denoting an improved adherence to the guidelines by the average cardiologist involved in the management of ACS patients in our country. Furthermore, in our study cohort, 27% of patients underwent PCI and 1% CABG, while when considering only the patients treated in hospitals with catheterization facilities, 54% underwent PCI and almost 2% CABG, respectively. The use of coronary interventions in our study cohort is considerably less frequent in comparison to the respective data reported in the second Euro Heart Survey on ACS (PCI in 57.8% of ST-elevation ACS and 37.1% of non ST-elevation ACS patients).[14] However, in our survey the percentage of patients following invasive management is underestimated, since we have not taken into consideration potential referrals from hospitals with no catheterization laboratory to those with catheterization facilities. Furthermore, the results of the Euro Heart Survey are hampered by limited representativeness, mainly associated with the voluntary participation of highly motivated centers, and the disproportionately high percentage of patients admitted to hospitals with on-site catheterization facilities (73%) and medical centers affiliated with academic institutions (53%).

In conclusion, the TARGET study was a multicenter, observational survey that depicted the epidemiological profile, the management practice and outcome of ACS patients in Greece. The alarmingly high rate of dyslipidemia, hypertension, smoking and diabetes remains a cause for concern and a challenge that needs to be tackled, since better control of cardiovascular risk factors is expected to have a favorable impact on the incidence of ACS. On the other hand, evidence-based medications are widely adopted in the everyday world, suggesting a minor gap between evidence and practice. Considerable room for improvement exists in minimizing pre-hospital delays and expanding the use of invasive management among ACS patients.

Acknowledgements

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