ORIGINAL ARTICLE

Epidemiological characteristics, management and early outcomes of acute coronary syndromes in Greece: The PHAETHON study

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Abstract *Introduction:* In view of recent therapeutic breakthroughs in acute coronary syndromes (ACS) and essential demographic and socioeconomic changes in Greece, we conducted the prospective, multi-center, nationwide PHAETHON study (An Epidemiological Cohort Study of Acute Coronary Syndromes in the Greek Population) that aimed to recruit a representative cohort of ACS patients and examine current management practices and patient prognosis.
Methods: The PHAETHON study was conducted from May 2012 to February 2014. We enrolled 800 consecutive ACS patients from 37 hospitals with a proportional representation of all types of hospitals and geographical areas. Patients were followed for a median period of 189 days. Outcome was assessed with a composite endpoint of death, myocardial infarction, stroke, urgent revascularization and urgent hospitalization for cardiovascular causes.
Results: The mean age of patients was 62.7 years (78% males). The majority of patients (n=411, 51%) presented with ST-elevation myocardial infarction (STEMI), whereas 389 patients presented with NSTEMI (n=303, 38%) or UA (n=86, 11%). Overall, 58.8% of the patients had hypertension, 26.5% were diabetic, 52.5% had dyslipidemia, 71.1% had a smoking history (current or past), 25.8% had a family history of coronary artery disease (CAD) and 24.1% had a prior history of CAD. In STEMI patients, 44.5% of patients were treated with thrombolysis, 38.9% underwent a coronary angiogram (34.1% were treated with primary percutaneous coronary intervention) and 16.5% did not receive urgent treatment. The pain-to-door time was 169 minutes. During hospitalization, 301 (38%) patients presented one or more complications, and 13 died (1.6%). During follow-up, 99 (12.6%) patients experienced the composite endpoint, and 21 died (2.7%).
Conclusions: The PHAETHON study provided valuable insights into the epidemiology, management and outcome of ACS patients in Greece. Management of ACS resembles the management observed in other European countries. However, several issues still to be addressed by public authorities for the timely and proper management of ACS.
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1. Introduction

Acute coronary syndromes (ACS) represent a challenging and demanding clinical problem. ACS comprise the majority of all acute medical admissions and encompass a high risk of in-hospital morbidity and mortality. Despite significant improvements in morbidity and mortality through the enhancement of treatment modalities in recent years, patients with ACS remain at high risk of recurrent ischemic events and death. These facts underscore the importance of proper and concise documentation of contemporary management and ACS prognosis at both international and national levels.[1]

Numerous epidemiological studies from European countries have led to insights regarding the prevalence, treatment and prognosis of ACS in Europe. These studies have also indicated geographic differences, disparities in dietary habits and the prevalence of cardiovascular risk factors and heterogeneity in the care and prognosis of patients with ACS across Europe.[2] Therefore, national surveys are thought to be indispensable to the epidemiology, treatment and prognosis of the everyday patient population. Furthermore, these surveys should incorporate a nationwide representative population and hospital sample to reflect everyday practice on ACS. Representativeness is of utmost importance, especially in countries with great diversity in geography and healthcare infrastructure, such as Greece. Nationwide surveys also comprise a pragmatic assessment of ACS management, rather than a highly controlled clinical setting, as the one utilized in randomized studies.[1]

During the previous decade, the findings of the prospective survey named GREECS[12] and the results of a large countrywide survey in Greece, the HELIOS study,[3] were published in 2005 and 2007, respectively.[3] However, in subsequent years, much has changed both in the

prevalence and management of ACS. Therefore, we conducted the PHAETHON study, an up-to-date sequel of the HELIOS study. The PHAETHON study aimed prospectively to provide further contemporary data concerning the epidemiological profile, management pattern and outcomes in a cohort of real-word, consecutive ACS patients included in a countrywide observational study in Greece.

2. Methods

2.1. Study population

The PHAETHON study was a prospective, multicenter, observational study that **enrolled consecutive patients** with a hospital discharge diagnosis of ACS [ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), unstable angina (UA)] at a total of 37 participating centers in Greece. The study was conducted from May 2012 to February 2014. Case definition was based on the 2012 consensus definition of myocardial infarction[4] and relevant European Guidelines.[5,6] To minimize systematic enrollment bias and to maximize the generalizability of our results, we recruited patients from centers with a representative geographical distribution, proportionally covering all regions in Greece. The majority of ACS patients are initially hospitalized in the cardiology departments of regional hospitals, and assuming that the number of ACS is proportional to the resident population older than 25 years in every geographical distribution, we calculated a certain number of consecutive ACS patients to be enrolled in the survey from each region, in proportion to the estimated population older than 25 years in each of the major geographical regions (Fig. 1). Furthermore, to avoid the caveat of overrepresentation of hospitals with catheterization facilities, we balanced patient inclusion from centers with and without revascularization capacity and other hospital characteristics (public and private, academic and non-academic, rural and urban hospitals). All patients were informed about the study and signed a written informed consent. The study was conducted according to the Declaration of Helsinki, the European Guidelines on Good Clinical Practice, and relevant national and regional authority requirements and ethics committees.

2.2. Measured variables

During hospitalization, a case report form was filled out for patients with a confirmed diagnosis of ACS. The case report included data on demographic (age, gender, height, weight, waist circumference, body mass index [BMI], educational level, marital and employment status), clinical (presentation and time of symptom onset, the selected means and duration of transportation to the hospital, medications used before admission), and electrocardiographic characteristics of the patients. All patients were questioned about their past medical cardiovascular and non-cardiovascular history and the prevalence of the following cardiovascular risk factors: hypertension (blood pressure $\geq$140/90 mmHg or treatment with antihypertensive agents), dyslipidemia (total cholesterol $\geq$190 mg/dL or treatment with hypolipidemic medications), diabetes mellitus, smoking status (history of smoking was established in current or ex-smokers), and family history of premature coronary artery disease (CAD). Metabolic syndromes were identified based on ATP III criteria. Data collection was based on standardized definitions.[7] Moreover, the case report included diagnostic and treatment modalities, in-hospital complications, and discharge status. Furthermore, we calculated the (Global Registry of Acute Coronary
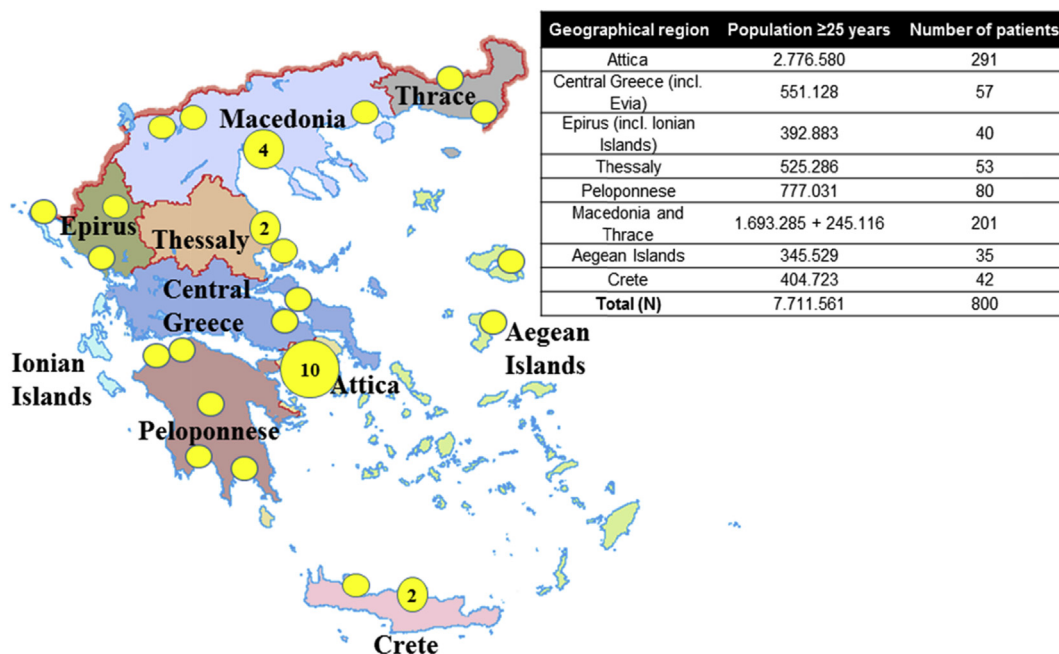

Geographical region	Population ≥25 years	Number of patients
Attica	2.776.580	291
Central Greece (incl. Evia)	551.128	57
Epirus (incl. Ionian Islands)	392.883	40
Thessaly	525.286	53
Peloponnese	777.031	80
Macedonia and Thrace	1.693.285 + 245.116	201
Aegean Islands	345.529	35
Crete	404.723	42
Total (N)	7.711.561	800

Figure 1 Geographical distribution of the participating centers and table with the number of participating patients from each geographical region.

Events) GRACE risk score for risk stratification of patients upon admission.[8,9]

The primary outcome of the study was the assessment of epidemiological characteristics, management and in-hospital mortality of ACS patients in Greece. The secondary outcome variable was the early prognosis (6 months) of ACS patients, which was investigated through a composite endpoint consisting of cardiovascular death, myocardial infarction, stroke/transient ischemic attack, urgent reperfusion [percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)] and urgent hospitalization due to cardiovascular causes. All patients were contacted by means of questionnaires or telephone interview. Data were confirmed and verified against hospital databases and medical records.

2.3. Statistical analysis

Continuous variables are presented as the mean $\pm$ SD, whereas non-normally distributed variables are presented as medians and interquartile ranges. We used Student's t tests for independent samples to compare means for normally distributed variables, Mann-Whitney tests for skewed variables and chi-square tests for qualitative variables. The Shapiro-Wilk test for normality was used to evaluate the t-test assumption. The natural logarithm of the time from symptoms to first medical contact was used because of its skewed distribution. A p value <0.05 was considered to be significant. Data analysis was performed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient population and initial presentation

We recruited 800 patients (mean age $=62.7\pm13.0$ years, 78.3% men). Regarding their diagnosis, the majority of patients (n$=$411, 51.38%) presented with ST-elevation myocardial infarction (STEMI), whereas 389 patients presented as NSTEMI (n$=$303, 37.88%) or UA (n$=$86, 10.75%). In Table 1, we report the baseline characteristics of patients in each ACS category. STEMI patients were younger (p$<$0.001) and had increased prevalence of smoking history (p$=$0.034) compared with non-STEMI and UA patients; however, no difference was found based on gender.

Regarding cardiovascular risk factors, STEMI patients had less probability of having hypertension, hypercholesterolemia, diabetes, metabolic syndrome and history of confirmed CAD compared with other ACS categories; however, the prevalence of family history of CAD was not significantly different between ACS categories (Table 1).

The majority of patients presented with chest pain (n$=$713, 89.1%). However, the patients also presented with one or more other symptoms such as chest discomfort radiating to arms, neck or jaw (n$=$461, 57.6%), nausea/vomiting (n$=$227, 28.4%), sweating (n$=$452, 56.5%), dizziness (n$=$182, 22.8%) or dyspnea (n$=$234, 29.3%).

The median duration between symptom onset and first medical contact (FMC), which is defined as the time of diagnostic electrocardiogram or the ambulance arrival, was equal to 169 min (IQR: 60–446 min), whereas the median duration of transfer to the hospital was 30 min (IQR: 15–45 min) for those patients (48%) who were transferred by emergency medical system (EMS, ambulance or helicopter) compared with 15 min (IQR: 10–30) for those (52%) who were transferred on their own means (taxi or car).

3.2. Management of STEMI patients

Most patients with STEMI were treated with thrombolysis (n$=$183, 44.5%), principally with tenecteplase (n$=$91, 49.7%) and reteplase (n$=$82, 44.8%). The median door-to-needle time was 30 min (IQR: 19–60). Thrombolysis was considered successful in more than four out of five STEMI patients (n$=$149, 81.4%). A small percentage (n$=$40, 26.8%) of the patients also underwent a coronary angiogram. In contrast, of 34 patients with unsuccessful thrombolysis, the majority of the patients (n$=$20, 58.8%) underwent coronary catheterization.

Table 1 Baseline characteristics according to acute coronary syndrome type at hospital admission.

Variable	STEMI (n$=$411)	Non-STEMI (n$=$303)	UA (n$=$86)	p-value
Age (years)	61$\pm$12	65$\pm$13	63$\pm$11	0.001
Gender, male (%)	327(79.6%)	231 (76.2%)	68 (79.1%)	0.557
Hypertension	218 (53.3%)	195 (64.5%)	57 (66.2%)	0.003
Hypercholesterolemia	194 (47.3%)	171 (56.8%)	56 (66.6%)	0.002
Diabetes	83 (20.3%)	108 (36.3%)	21 (24.7%)	$<$0.001
Family history of CAD	105 (25.7%)	73 (24.4%)	28 (32.5%)	0.282
History of CAD	57 (13.9%)	99 (33.0%)	36 (41.8%)	$<$0.001
Smokers (past or current)	308 (74.9%)	200 (66.0%)	61 (70.9%)	0.034
Body mass index (kg/m^2)	28.2$\pm$4.8	28.5$\pm$5.1	28.1$\pm$4.5	0.914
Waist (cm)*	101.4$\pm$13.8	102.4$\pm$13.8	99.5$\pm$12.8	0.257
Metabolic syndrome*	178 (53%)	184 (68%)	41 (53%)	$<$0.001
Probability of in-hospital mortality based on GRACE (%)¶	2.25 (1.25–4.18)	2.36 (1.22–4.76)	0.80 (0.49–1.37)	$<$0.001
Probability of 6-month mortality based on GRACE (%)¶	3.17 (1.77–5.66)	5.32 (2.55–9.70)	2.37 (1.48–4.80)	$<$0.001

*n$=$684, ¶n$=$682.
STEMI$=$ST-elevation myocardial infarction, NSTEMI$=$Non-ST elevation myocardial infarction, UA$=$unstable angina, CAD$=$Coronary Artery Disease.

Many patients with STEMI underwent coronary angiography (n=160, 38.9%), and 140 (34.1%) of them also underwent primary PCI. The median door-to-balloon time was 90 min (IQR: 45–135). For the remaining 20 patients, 1 underwent rescue PCI, 8 underwent elective PCI and 11 did not undergo any PCI. In most cases, the femoral approach was preferred (n=125, 78.1%) compared with the radial approach (n=32, 20%).

To ensure reliable estimates of average PCI-related delays at an individual participating hospital, inclusion in this analysis required a minimum number of STEMI patients. Specifically, at least 10 STEMI patients during the study, including at least 5 patients treated with primary PCI and 5 with fibrinolytic therapy, were required. These criteria yielded 4 hospitals that were eligible for analysis. A given hospital's PCI-related delay or its median time delay in performing primary PCI compared with administering fibrinolytic therapy was calculated by subtracting the median door-to-needle time from the median door-to-balloon time at each hospital. Finally, the mean median PCI-related time delay was estimated at 56.2 minutes.

In 68 STEMI (16.5%) patients, no immediate revascularization treatment was applied, and in several cases, more than one reason was reported. Regarding thrombolysis, delayed hospital admission was the most common reason (n=43, 63.2%), followed by age (n=17, 25%), active bleeding or prone to bleeding status (n=4, 5.9%), history of intracranial hemorrhage or intracranial disease or ischemic attack (n=2, 2.9%) and suspected aortic dissection (n=1, 1.5%), while in 9 cases, no apparent reason was reported (n=9, 13.2%). Regarding coronary angiography or PCI, unavailability was the most common reason (n=60, 88.2%), followed by delayed hospital admission (n=14, 20.6%) and increased risk of complications (n=4, 5.9%).

3.3. Management of NSTEMI/UA patients

In total, 151 (39%) patients with NSTEMI/UA underwent a coronary angiogram in the hospital that the patients were initially admitted or were transferred to another hospital for coronary angiography, and 92 of the patients (24%) underwent PCI. The median time from admission to coronary angiography was 43.5 hours (IQR: 13.0–84.0). The remaining patients did not undergo coronary angiography during hospitalization (n=238, 61%). The femoral approach was preferred (n=108, 71.5%) compared with the radial approach (n=27, 17.9%), whereas in the remaining patients, relevant data were not reported.

A small proportion (n=19, 4.9%) of patients who were admitted to the hospital with NSTEMI/UA underwent stress testing, primarily a treadmill stress test (n=15) and a single-photon emission computed tomography imaging test (n=4); however, none of the patients underwent a stress echo. In 12 cases, the stress test showed ischemia or a high likelihood of ischemia; in 5 cases, the test was negative; and in 2 cases, the results were not reported.

3.4. In-hospital complications

In total, the in-hospital events are presented in Table 2. During the hospitalization of 301 (38%) patients, at least

Table 2	In-hospital events.
Event	n, (%)
Death	13 (1.63%)
Angina recurrence	122 (15.3%)
Re-infarction	9 (1.1%)
Heart Failure (defined as >Killip 1)	92 (11.5%)
Pulmonary edema (Killip 3)	38 (4.8%)
Cardiogenic shock (Killip 4)	23 (2.9%)
Mechanic complications	2 (0.3%)
Asystolic arrest	9 (1.1%)
Pulseless electrical activity	5 (0.6%)
2nd/3rd degree AV block	19 (2.4%)
Non Sustained Ventricular Tachycardia	67 (8.4%)
Sustained Ventricular Tachycardia	13 (1.6%)
Ventricular Fibrillation	28 (3.5%)
Atrial Fibrillation/flutter	52 (6.5%)
Stroke/TIA	4 (0.5%)
Major hemorrhagic event (TIMI)	2 (0.3%)
Urgent CABG	5 (0.6%)
LV thrombus	3 (0.4%)
Pericarditis	1 (0.1%)

AV=Atrioventricular, TIA=Transient Ischemic attack, CABG=Coronary artery bypass graft, TIMI=Thrombolysis In Myocardial Infarction.

one in-hospital event occurred, and 13 patients (1.63%) with ACS died. STEMI patients had a higher incidence of in-hospital complications compared with NSTEMI/UA patients. Specifically, during hospitalization, more STEMI patients compared with NSTEMI/UA had heart failure (16% vs 7%, p<0.001), cardiogenic shock (4% vs 2%, p=0.028), asystole (2% vs 0%, p=0.024), pulseless electrical activity (1% vs 0%, p=0.029), 2nd/3rd degree atrio-ventricular block (3% vs 1%, p=0.049), non-sustained ventricular tachycardia (14% vs 2%, p<0.001), sustained ventricular tachycardia (3% vs 0%, p=0.003), and ventricular fibrillation (6% vs 1%, p<0.001). No statistically significant differences were found between the 2 groups in the remaining list of complications, including death.

3.5. Hospital discharge

In total, 787 patients were discharged. Of the 714 patients with MI (STEMI or NSTEMI), and according to the international definition of MI (n=670), the majority was classified as type 1 (n=619, 92%) followed by type 2 (n=44, 7%) and type 4b (n=7, 1%). The median duration of hospitalization in the Coronary Care Unit was 3 days (IQR: 2–4). The median duration of hospitalization was 5 days (IQR: 3.4–6.7). A significant proportion of the discharged patients (n=205, 26.0%) was referred to another hospital for further treatment.

Regarding the New York Heart Association (NYHA) classifications at hospital discharge, the majority of the patients were at NYHA I (n=578, 73.4%), followed by NYHA II (n=155, 19.7%), NYHA III (n=18, 2.3%) and NYHA IV (n=4, 0.5%). Based on the estimated ejection fraction (EF) by echocardiography according to the Simpson rule, 88 (11.2%)

Table 3 Medication at hospital discharge (n=787) and at follow-up (n=767).

	At hospital discharge N (%)	At follow-up N (%)
Anti-hypertensive drugs/Anti-arrhythmic drugs		
Beta-blockers	676 (85.9%)	646 (84.2%)
Calcium channels blockers	82 (10.4%)	90 (13%)
Nitrates	264 (33.5%)	108 (14.1%)
Aldosterone receptor blockers	92 (11.7%)	81 (10.6%)
Angiotensin converting enzyme inhibitors	397 (50.4%)	327 (42.6%)
Angiotensin receptor II blockers	159 (20.2%)	183 (23.9%)
Other anti-hypertensive drugs	9 (1.1%)	9 (1.2%)
Anti-arrhythmic drugs	33 (4.2%)	23 (3.0%)
Digitalis	9 (1.1%)	7 (0.9%)
Diuretics	178 (22.6%)	190 (24.8%)
Ivabradine	38 (4.8%)	30 (3.9%)
Anti-diabetic drugs		
Insulin	60 (7.6%)	42 (5.5%)
Per os anti-diabetic drugs	129 (16.4%)	122 (15.9%)
Anticoagulants/Antiplatelets		
Vitamin K antagonists	34 (4.3%)	47 (6.1%)
Dabigatran	1 (0.1%)	1 (0.1%)
Rivaroxaban	0 (0%)	0 (0%)
Low-molecular weight heparin	66 (8.4%)	2 (0.3%)
Aspirin	741 (94.2%)	700 (91.3%)
Clopidogrel	535 (68.0%)	483 (63.0)
Prasugrel	49 (6.2%)	44 (5.7%)
Ticagrelor	133 (16.9%)	110 (14.3%)
Triflusal	10 (1.6%)	6 (0.8%)
Hypolidemic drugs		
Statins	759 (96.4%)	710 (92.6%)
Ezetimibe	33 (4.2%)	32 (4.2%)
Niacin	2 (0.3%)	1 (0.1%)
Fibrates	2 (0.3%)	7 (0.9%)
Omega-3	91 (11.6%)	38 (5.0%)

patients at discharge had reduced EF (<40%) and of whom 75 (8.5%) did not have known heart failure at admission. In Table 3, we report the medications at hospital discharge and at follow-up.

3.6. Follow-up

Of the 787 patients who were discharged, 5 were lost in follow-up, and the exact date of follow-up was not reported for 5 patients. The patients were followed for a median time of 189 days (IQR: 180–212). During follow-up, in 99 (12.6%) patients, at least one major adverse cardiac event (MACE) occurred, and 21 died (2.7%). Specifically, 5 patients suffered a stroke (0.6%), 9 patients suffered a myocardial infarction (1.1%), 13 patients required urgent coronary revascularization (1.7%) and 80 patients were hospitalized (10.2%) urgently for cardiovascular causes. NSTEMI/UA patients showed a trend for a higher incidence of MACE compared with STEMI patients who was not statistically significant (14.7% vs 10.7%, p=0.09). Concerning each endpoint separately, only stroke was statistically more frequent in NSTEMI/UA patients compared with STEMI patients (1.3% vs 0%, p=0.021).

4. Discussion

The PHAETHON study was designed to include a representative sample of patients with ACS on a nationwide basis, aiming to continue and advance the findings from the "parent" study HELIOS that was published 8 years ago. The prospective, multicenter, observational PHAETHON study, which enrolled consecutive patients with a hospital discharge diagnosis of ACS, was conducted to provide data regarding the epidemiological pattern, the management and the outcome of patients with ACS throughout Greece in real-time hospital conditions and not in the "protected" setting of randomized clinical trials where tertiary and university hospitals are overrepresented.

4.1. Baseline characteristics and initial presentation

Several large-scale, countrywide (nationwide), population studies in the last 20 years have examined the epidemiological characteristics of patients either with acute MI or, more recently, ACS. These population studies include the Hellenic study of acute MI, which recruited almost 7500

patients with MI from almost all the country-wide hospitals in the mid-1990s,[10] the CARDIO2000 case-control study of acute coronary syndromes,[11] the prospective GREECS study that estimated the crude annual incidence rate of ACS in 22.6 per 10,000 people,[12] the TARGET study,[13] the APTOR II study that focused mainly on patients undergoing coronary intervention and their antiplatelet therapy,[14] the Stent For Life initiative that investigated the management of STEMI patients[15] and the HELIOS study.[3] Interestingly, in several cases, data from these studies were used in larger European surveys.[2,16–20]

The mean presentation age of this study is similar or somewhat lower compared with older surveys. This different may be attributed to the higher prevalence of cardiovascular risk factors as well as our better understanding of and ability to detect ACS (i.e., with the use of high sensitivity troponin).[16] Both genders have similar representation in STEMI, as well in NSTEMI/UA ACS. Smokers and younger individuals as observed in the HELIOS study still have a higher risk for STEMI compared with NSTEMI/UA, implying a much more aggressive cardiac phenotype in young smokers that relates to higher in-hospital mortality.[10] In contrast, a history of CAD, hypertension, diabetes, metabolic syndrome and hypercholesterolemia are more common risk factors in NSTEMI/UA compared with STEMI patients, implying a more indolent cardiac phenotype that relates to more severe complications during follow-up after the initial event, especially if these risk factors are not well-controlled.

The study elucidates the clinical characteristics of the "real-world" ACS patient and unveils a deteriorating burden of cardiovascular risk factors among ACS patients in Greece. Despite a potential difference in definitions from earlier studies, the prevalence of the main cardiovascular risk factors such as hypertension (59%), hypercholesterolemia (53%), smoking (71%) and diabetes (27%) remains similar to those previously presented, especially in the HELIOS study.[3] However, the percentage of patients with a history of CAD has considerably increased from 18% in HELIOS to 24% in our survey, which was also confirmed by the TARGET study.[13] This finding stresses the increased cardiovascular risk and overall economic impact due to frequent hospitalizations of patients with CAD, as well as the need for better implementation of secondary prevention measures in these patients. Furthermore, in the present study, patients had a higher BMI compared with earlier studies, and more than 1 out of 2 ACS patients (59%) had a metabolic syndrome. This percentage is much higher to the one (36.2%) described in the CARDIO2000 study,[17] underscoring the growth of the obesity epidemic, which is attributed to lifestyle and nutritional changes. These findings are essential for physicians and healthcare policymakers who have the challenging and provoking task of reducing the obesity epidemic, improper nutrition and sedentary lifestyle as well as the prevention and early identification of metabolic syndromes.

In this study, the time from symptom onset to FMC (168 min) was shorter than the time described in HELIOS study[3] (180 min) and slightly longer than the time describe in the Stent for Life study[15] (140 min), demonstrating the need for better patient education, as well as better organization of the prehospital service. This finding is further confirmed by the fact that in our study, the patients who chose to use their own means of transportation instead of the EMS had shorter transportation times, which is in accordance with TARGET study[13] that showed that the mean waiting time for and ambulance was approximately 20 minutes and stresses the need for better organization and increase in manpower of the EMS. Nevertheless, 1 out of 2 patients used the EMS, a percentage that is substantially higher than the 38% percent in STEMI patients in the Stent for Life study.[15]

4.2. Management of STEMI and NSTEMI/UA patients

Over the past several years, a substantial improvement has been observed in the management of ACS patients. The most important element of treatment in STEMI patients still is the timely implementation of reperfusion therapy, by either PCI or fibrinolysis, while in NSTEMI/UA patients an earlier invasive strategy has been advocated. As previously described,[15] a clear increase was observed in the number of primary PCI procedures in recent years in Greece. This increase is linked to an impressive decrease of the no-reperfusion option for STEMI. Specifically, in the earlier HELIOS study,[3] 9% underwent primary PCI, 50% underwent fibrinolysis and 41% received no reperfusion therapy, while in the more recent Stent For Life study,[15] 32% underwent primary PCI, 40% underwent fibrinolysis and 28% received no reperfusion therapy. Similarly, we have shown similar and somewhat better percentages in the management of STEMI patients with 34% undergoing primary PCI (39% underwent coronary angiogram), 44.5% undergoing fibrinolysis and only 16.5% receiving no reperfusion therapy, implying an improvement in the management of STEMI patients. However, the main reasons for no reperfusion therapy remain delayed hospital admission and unavailability of primary PCI, entailing the improvement of the infrastructure and participation of PCI networks in a nationwide scale.

As far as NSTEMI/UA patients are concerned, a more invasive approach was observed in approximately 40% of patients who underwent coronary angiography in a median time period of less than 2 days, with 24% of the patients also undergoing PCI. This finding is an important advancement since the HELIOS study[3] in which only 6.1% of NSTEMI patients underwent coronary angiography and PCI. The non-invasive approach of stress testing is not preferred during hospitalization for an ACS, and in most cases, is not crucial for the management of the NSTEMI/UA patient. Therefore, in the current practice environment where coronary catheterization is by far the initial diagnostic modality in NSTEMI/UA patients, the role of stress testing warrants further investigation.[18]

Additionally, an essential differentiation from earlier studies is that the percentage of patients undergoing coronary angiogram through the radial approach has increased significantly (approximately 1 out of 5 patients for all ACS patients) compared with the 2.3% reported in the APTOR II study,[14] showing an important progress in technical skills in Greece as well as elaborating the lower hospitalization time.[19]

4.3. In-hospital complications and mortality

In our study, a relatively high rate of in-hospital complications was accompanied by a relatively low rate of in-

hospital mortality. This discrepancy has many plausible explanations. First, the high rate of in-hospital complications can be partially explained by the extensive list of minor complications (e.g., atrial fibrillation and angina) as well as major in-hospital complications (e.g., asystole and ventricular fibrillation) that was not reported in other relevant studies.[3,13] Moreover, the in-hospital mortality observed (1.63%) was similar to the one estimated by the GRACE score for in-hospital mortality (2.05%), suggesting a small likelihood of selection bias and unreported or missed events. Furthermore, in our study, most of the patients underwent reperfusion therapy or were promptly transferred to larger hospitals,[20] diminishing the risk of in-hospital mortality, compared with older studies that had high rates of patients with no reperfusion who were conservatively managed. Invasive management could also explain the higher rate of minor complications compared with death because most invasive measures may have averted death as a complication at the expense of minor complications. All of these factors elucidate the lower mortality rate observed compared with the earlier HELIOS[3] (7.7% for the total patient population, 8.9% for STEMI and 5.8% for NSTEMI patients) and STENT FOR LIFE[15] (4.7% for STEMI patients undergoing primary PCI, 4% for NSTEMI and 11% no reperfusion patients) studies. However, in more recent studies, the in-hospital mortality is similar to the one observed in PHAETHON,[13] indicating a slow but steady reduction of in-hospital mortality in Greece, as well as in Europe.[18,21] Notably, in accordance with larger surveys, we also found a higher risk of in-hospital complications in patients with STEMI compared with NSTEMI/UA, confirming their worse in-hospital prognosis.[22]

4.4. Hospital discharge and short-term follow-up

For the first time in Greece, an assessment and classification of myocardial infarction was performed according to the recent universal definition of MI.[4] Our findings confirm studies in other European countries that have shown that despite the extremely high percentage of type 1 MI (approximately 9 out of 10 cases of MI), a small but substantial percentage of patients with type 2 MI exists between 5% and 10%.[23] This finding is of extreme importance because it is now well established that these patients have a higher risk for future events and should be closely followed and intensively managed post discharge.[24]

Furthermore, primarily due to the immediate invasive treatment as well as the timely transfer to tertiary hospital, days of hospitalization have significantly decreased compared with the TARGET study[13] in which patients were hospitalized for approximately 7 days. However, the application of more tight economic boundaries in hospitalizations has also contributed to this decrease.

The use of beta-blockers, aspirin, statins and angiotensin converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARBs) at discharge has been utilized for the evaluation of the standard of care provided and is considered as an indicator of hospital quality performance. In our survey, aspirin was used in 94% of patients at discharge, while beta-blockers and ACE inhibitors or ARBs were administered to 86% and 71%, respectively.

Concerning the use of statins, an impressive 96% of our patients received statins upon discharge. Notably, in our survey, we found an increased rate of use of most types of evidence-based medications compared with the HELIOS study.[3] Upon discharge, a greater proportion of our patients were prescribed antiplatelets, beta-blockers and statins in comparison to the respective ratios reported in the HELIOS study[3]; however, a slight decrease in the use of ACE inhibitors and ARBs was noted. Importantly, this is the first nationwide study on ACS that shows the entrance of newer antiplatelets in the management of ACS patients. Specifically, in accordance with recent European guidelines, the use of primarily ticagrelor (17%) and, to a lesser extent, prasugrel (6%), has been introduced in clinical practice, leading to a reduction of the use of clopidogrel compared with the results from the TARGET study (66% from 84%).[13] These rates are lower than the ones reported for the newer antiplatelets in the GRAPE study.[25] However, in GRAPE study, only patients with ACS from tertiary hospitals undergoing PCI were included. Thus, we believe that our estimates are closer to the real-world ACS patient and that these estimates underscore the need for better adherence to guidelines concerning antiplatelet use. Thus, the quality measures for the use of evidence-based medicine that have been shown to improve patient prognosis demonstrate a satisfactory hospital performance, which indicates a substantial improvement in the management of patients and better adherence to the current guidelines.

Regarding follow-up, our short-term mortality is somewhat lower than the one presented in earlier studies; however, the mortality is still similar to the one expected according to the GRACE score (2.7% compared to 3.5%, respectively). Furthermore, the validity of our follow-up data is also confirmed by the fact that NSTEMI/UA patients exhibited a trend for higher incidence compared with STEMI patients, which is in accordance with larger surveys.

4.5. Limitations

The study has the limitations of an observational study. Although a large number of consecutive ACS patients were enrolled, reflecting current practice, not all patients with ACS admitted to those hospitals were included. Thus, a small likelihood of selection bias cannot be excluded. However, in contrast to most previous surveys or registries, we enrolled a representative sample from the majority of Greek hospitals with cardiology departments, with a balanced representation of invasive and non-invasive hospitals, of urban and rural areas. Furthermore, the majority of our findings were confirmed by larger surveys, suggetsing that we managed to adequately reflect real-world practice.

5. Conclusions

The PHAETHON study was a multicenter, observational survey that illustrated the epidemiological characteristics, the management and the outcome of ACS patients in Greece. Considerable research over the last several years has produced a better understanding of and compliance to

evidenced-based management strategies, such as the timely use of invasive management, which has led to significant improvements in the management and outcome of ACS patients, despite the lack of improvement of the cardiovascular profile of ACS patients. However, considerable room for improvement still remains, and many challenges need to be addressed to improve the prognosis of ACS patients in Greece.

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Acknowledgments

Appendix

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References

1. Pipilis AG, Paschidi MD, Andrikopoulos GK, Goudevenos JA, Working Group on Clinical Epidemiology, Prevention and Metabolic Syndrome of the Hellenic Cardiological Society. Seven plus one reasons for surveys of acute myocardial infarction in Greece. *Hellenic J Cardiol*. 2006;47:194—197.
2. André R, Bongard V, Elosua R, et al. International differences in acute coronary syndrome patients' baseline characteristics, clinical management and outcomes in Western Europe: the EURHOBOP study. *Heart*. 2014;100:1201—1207.
3. Andrikopoulos G, Pipilis A, Goudevenos J, et al. Epidemiological characteristics, management and early outcome of acute myocardial infarction in Greece: the HELlenic Infarction Observation Study. *Hellenic J Cardiol*. 2007;48:325—334.
4. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33:2551—2567.
5. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569—2619.
6. Hamm CW, Bassand JP, Agewall S, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:2999—3054.

7. Weintraub WS, Karlsberg RP, Tcheng JE, et al. ACCF/AHA 2011 key data elements and definitions of a base cardiovascular vocabulary for electronic health records: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards. *Circulation*. 2011;124:103—123.

8. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163:2345—2353.

9. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006;333:1091.

10. Andrikopoulos GK, Richter DJ, Dilaveris PE, et al. In-hospital mortality of habitual cigarette smokers after acute myocardial infarction; the "smoker's paradox" in a countrywide study. *Eur Heart J*. 2001;22:776—784.

11. Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C, Toutouzas P. Risk stratification of coronary heart disease in Greece: final results from the CARDIO2000 epidemiological study. *Prev Med*. 2002;35:548—556.

12. Pitsavos C, Panagiotakos DB, Antonoulas A, et al. Epidemiology of acute coronary syndromes in a Mediterranean country; aims, design and baseline characteristics of the Greek study of acute coronary syndromes (GREECS). *BMC Public Health*. 2005;5:23.

13. Andrikopoulos G, Tzeis S, Mantas I, et al. Epidemiological characteristics and in-hospital management of acute coronary syndrome patients in Greece: results from the TARGET study. *Hellenic J Cardiol*. 2012;53:33—40.

14. Pavlides G, Drossinos V, Dafni C, et al. Current management and quality of life of patients with acute coronary syndrome undergoing percutaneous coronary intervention in Greece: 12-month results from antiplatelet therapy observational study II (APTOR II). *Hellenic J Cardiol*. 2013;54:255—263.

15. Kanakakis J, Ntalianis A, Papaioannou G, Hourdaki S, Parharidis G. Stent for life initiative—the Greek experience. *EuroIntervention*. 2012;8(suppl P):P116—P120.

16. Twerenbold R, Jaffe A, Reichlin T, Reiter M, Mueller C. High-sensitive troponin T measurements: what do we gain and what are the challenges? *Eur Heart J*. 2012;33:579—586.

17. Pitsavos C, Panagiotakos DB, Chrysohoou C, et al. The adoption of Mediterranean diet attenuates the development of acute coronary syndromes in people with the metabolic syndrome. *Nutr J*. 2003;2:1.

18. Mehta RH, Rao SV, Ohman EM, et al. Variation in the use of stress testing and outcomes in patients with non-ST-elevation acute coronary syndromes: insights from GUSTO IIb. *Eur Heart J*. 2008;29:880—887.

19. Lee MS, Wolfe M, Stone GW. Transradial versus transfemoral percutaneous coronary intervention in acute coronary syndromes: re-evaluation of the current body of evidence. *JACC Cardiovasc Interv*. 2013;6:1149—1152.

20. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European society of cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35:2541—2619.

21. Chung SC, Gedeborg R, Nicholas O, et al. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. *Lancet*. 2014;383:1305—1312.

22. Montalescot G, Dallongeville J, Van Belle E, et al. STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry). *Eur Heart J*. 2007;28:1409—1417.

23. Baron T, Hambraeus K, Sundström J, Erlinge D, Jernberg T, Lindahl B, TOTAL-AMI study group. Type 2 myocardial infarction in clinical practice. *Heart*. 2015;101:101—106.

24. Saaby L, Poulsen TS, Diederichsen AC, et al. Mortality rate in type 2 myocardial infarction: observations from an unselected hospital cohort. *Am J Med*. 2014;127:295—302.

25. Alexopoulos D, Goudevenos JA, Xanthopoulou I, et al. Implementation of contemporary oral antiplatelet treatment guidelines in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a report from the GReek AntiPlatelet rEgistry (GRAPE). *Int J Cardiol*. 2013;168:5329—5335.