ORIGINAL ARTICLE

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

G. Andrikopoulos a,*, D. Terentes-Printzios b, S. Tzeis a, C. Vlachopoulos b, C. Varounis c, N. Nikas d, J. Lekakis c, D. Stakos e, S. Lymeri f, D. Symeonidis g, D. Chriossos h, C. Kyprizidis i, D. Alexopoulos j, S. Zombolos k, S. Foussas l, A. Kranidis m, K. Oikonomou n, V. Vasilikos o, p, P. Andronikos q, A. Demitzakis r, D. Richter s, N. Fragakis t, I. Styliadis u, S. Mavridis v, C. Stefanadis b, P. Vardas w

a Henry Dunant Hospital Center, Athens, Greece
b 1st Cardiology Department, Hippokration Hospital, University of Athens Medical School, Greece
c University of Athens Medical School, Attikon University Hospital, Athens, Greece
d AstraZeneca SA, Medical Department, Athens, Greece
e Cardiology Clinic, Democritus University of Thrace, Alexandroupolis, Greece
f Cardiology Department, Sotiria Chest Diseases Hospital, Athens, Greece
g Cardiology Department, General Hospital of Kavala, Kavala, Greece
h Cardiology Department, Tripoli General Hospital, Tripoli, Greece
i Department of Cardiology, 2nd IKA Hospital, Thessaloniki, Greece
j Department of Cardiology, Patras University Hospital, Patras, Greece
k Department of Cardiology, General Hospital of Messinia, Kalamata, Greece
l Cardiology Department, Tzaneio State Hospital, Piraeus, Greece
m Cardiology Department, Western Attica General Hospital of Athens, Greece
n Cardiology Department, General Hospital of Edessa, Edessa, Greece
o First Department of Cardiology, AHEPA University Hospital, Aristotle University Medical School, Thessaloniki, Greece
p Third Department of Cardiology, Hippokration University Hospital, Aristotle University Medical School, Thessaloniki, Greece
q Department of Cardiology, Vostanion Hospital, Mytilini, Greece
r Department of Cardiology, Venizello General Hospital, Crete, Greece
s Second Department of Cardiology, Athens Euroclinic, Greece

* Corresponding author. George Andrikopoulos, 18 Parmenionos st. 13676, Thrikomakedones, Greece. Tel.: +30 6977285178.
E-mail addresses: andrikop@hotmail.com (G. Andrikopoulos).
Peer review under responsibility of Hellenic Cardiological Society.

http://dx.doi.org/10.1016/j.hjc.2016.06.003
1109-9666/© 2016 Hellenic Cardiological Society. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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.3

During the previous decade, the findings of the prospective survey named GREECS12 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 and relevant European Guidelines. 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 \( \geq 140/90 \text{ mmHg} \) or treatment with antihypertensive agents), dyslipidemia (total cholesterol \( \geq 190 \text{ mg/dL} \) 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. 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 distribution of the participating centers and table with the number of participating patients from each geographical region.](image-url)
Events) GRACE risk score for risk stratification of patients upon admission.6,9

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 ± 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 test assumption. The natural logarithm of the time from symptoms to first medical contact was used because of its test assumption. 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. Results

3.1. Patient population and initial presentation

We recruited 800 patients (mean age = 62.7 ± 13.0 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>
<thead>
<tr>
<th>Variable</th>
<th>STEMI (n = 411)</th>
<th>Non-STEMI (n = 303)</th>
<th>UA (n = 86)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 12</td>
<td>65 ± 13</td>
<td>63 ± 11</td>
<td>0.001</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>327 (79.6%)</td>
<td>231 (76.2%)</td>
<td>68 (79.1%)</td>
<td>0.557</td>
</tr>
<tr>
<td>Hypertension</td>
<td>218 (53.3%)</td>
<td>195 (64.5%)</td>
<td>57 (66.2%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>194 (47.3%)</td>
<td>171 (56.8%)</td>
<td>56 (66.6%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>83 (20.3%)</td>
<td>108 (36.3%)</td>
<td>21 (24.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>105 (25.7%)</td>
<td>73 (24.4%)</td>
<td>28 (32.5%)</td>
<td>0.282</td>
</tr>
<tr>
<td>History of CAD</td>
<td>57 (13.9%)</td>
<td>99 (33.0%)</td>
<td>36 (41.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smokers (past or current)</td>
<td>308 (74.9%)</td>
<td>200 (66.0%)</td>
<td>61 (70.9%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.2 ± 4.8</td>
<td>28.5 ± 5.1</td>
<td>28.1 ± 4.5</td>
<td>0.914</td>
</tr>
<tr>
<td>Waist (cm)*</td>
<td>101.4 ± 13.8</td>
<td>102.4 ± 13.8</td>
<td>99.5 ± 12.8</td>
<td>0.257</td>
</tr>
<tr>
<td>Metabolic syndrome*</td>
<td>178 (53%)</td>
<td>184 (68%)</td>
<td>41 (53%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Probability of in-hospital mortality based on GRACE (%)*</td>
<td>2.25 (1.25–4.18)</td>
<td>2.36 (1.22–4.76)</td>
<td>0.80 (0.49–1.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Probability of 6-month mortality based on GRACE (%)*</td>
<td>3.17 (1.77–5.66)</td>
<td>5.32 (2.55–9.70)</td>
<td>2.37 (1.48–4.80)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* 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 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.

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

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

### 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 \((11.2\%)\)
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, the CARDIO2000 case-control study of acute coronary syndromes, the prospective GRECS study that estimated the crude annual incidence rate of ACS in 22.6 per 10,000 people, the TARGET study, the APTOR II study that focused mainly on patients undergoing coronary intervention and their antiplatelet therapy, the Stent For Life initiative that investigated the management of STEMI patients and the HELIOS study. Interestingly, in several cases, data from these studies were used in larger European surveys.

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. 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. 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 current study, patients had a higher BMI compared with earlier studies, and more ACS patients (59%) had a metabolic syndrome. This percentage is much higher to the one (36.2%) described in the CARDIO2000 study, 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 (180 min) and slightly longer than the time describe in the Stent for Life study (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 that showed that the mean waiting time for 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.

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, 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, 9% underwent primary PCI, 50% underwent fibrinolysis and 41% received no reperfusion therapy, while in the more recent Stent For Life study, 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 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.

Additionally, an essential differentiation from earlier studies is that the percentage of patients undergoing coronary angiography 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, showing an important progress in technical skills in Greece as well as elaborating the lower hospitalization time.

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. 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, 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 study (7.7% for the total patient population, 8.9% for STEMI and 5.8% for NSTEMI patients) and STENT FOR LIFE (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, indicating a slow but steady reduction of in-hospital mortality in Greece, as well as in Europe. 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.

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. 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%. 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.

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 in which patients were hospitalized for approximately 7 days. However, the application of more tight economic boundaries in hospitals 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. Upon discharge, a greater proportion of our patients were prescribed antiplatelet agents, beta-blockers and statins in comparison to the respective ratios reported in the HELIOS study; 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 antiplatelet agents in the management of ACS patients. Specifically, in accordance with recent European guidelines, the use of principally 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%). These rates are lower than the ones reported for the newer antiplatelet agents in the GRAPE study. 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, suggesting 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.

Financial Disclosures

The study was supported by a grant from AstraZeneca. This work was undertaken and supported by the Hellenic Cardiovascular Research Society.

Acknowledgments

The study was supported by AstraZeneca. This work was undertaken and supported by the Hellenic Cardiovascular Research Society. We are indebted to all the cardiologists and to the directors of the Cardiac departments that participated in the study. The names of the study investigators are listed in the Appendix.

Appendix

Principal investigators: Professor Panos Vardas, Dr. George Andrikopoulos

Study coordinators: Stylianos Tzeis, Dimitrios Terentes-Printzios

Participating centers and investigators

5. General Hospital Larissa: K. Ntoulas, F. Vasiliou.
6. AHEPA University Hospital, Thessaloniki: A. Mega-risiotou, K. Dimitriou, V. Vasilikos.
12. Attikon University Hospital, Athens: F. Kolokathis, I. Koniali, E. Ilidromitis.
13. Papageorgiou General Hospital, Thessaloniki: D. Eftimiou V. Sachpekidis, I. Kaprinos.
15. Western Attica General Hospital of Athens, Attica: D. Kontogianni, A. Kranidis.
16. 2nd IKA Hospital, Thessaloniki: C. Kyprizidis.
17. Bodosakeio General Hospital of Ptolemaida: S. Lampropoulos.
18. Sotiria Thoracic Diseases Hospital, Athens: N. Marinakis, S. Lymeri.
24. Konstantopoulo General Hospital, Athens: A. Andriotis, S. Patsilinakos.
27. General Hospital of Preveza: D. Padazis, G. Sakka.
28. General Hospital of Thiva: M. Scoubourdis.
29. University Hospital of Alexandroupolis: D. Stakos.
31. General Hospital of Aigio: A. Ampousamala, I. Siclimiris, I. Stiladis
33. University Hospital of Larissa: M. Dalapaxsa, F. Tripiskiadis.
35. Tzaneio General Hospital of Piraues: A. Destounis, S. Foussas.
37. General Hospital of Tripoli: A. Giannoulis, D. Chrissos.

References


