ISCHEMIC HEART DISEASE

Clinical Characteristics, Prognosis, and Variability in the Management of Non-ST-Segment Elevation Acute Coronary Syndromes. Data From the PEPA Registry

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Objectives. To assess the clinical characteristics and inter-hospital variability in the treatment and prognosis of patients with non-ST-segment elevation acute coronary syndromes.

Patients and method. Data from the PEPA study, a prospective registry that enrolled 4,115 patients in 18 Spanish hospitals, were analyzed.

Results. The mean age of the patients enrolled was 65 years, 33% were women, and 26% had diabetes. Large differences were observed in the clinical profile of patients admitted to different centers, especially relative the history of previous disease, prior coronary revascularization, and co-morbidity. Antiplatelet treatment was used in 93% of patients, heparin in 45%, beta-blockers in 42%, nitrates in 67%, and calcium antagonists in 46%. During hospitalization, exercise stress testing was performed in 37% of patients, coronary angiography in 32%, coronary angioplasty in 9%, and coronary surgery in 4%. Inter-hospital variability was minimal for the use of antiplatelet agents, wide for the use of heparin and beta-blockers, and huge for the use of revascularization procedures. Mortality and the incidence of death or myocardial infarction were 2.6% and 4.4% during hospitalization, and 4.6% and 8% at 3 months, with wide inter-hospital variability. These differences were not significant once adjusted for clinical characteristics and the treatment received at admission.

Conclusions. Patients with non-ST-segment elevation acute coronary syndromes represent an heterogeneous group with a high incidence of complications. Pharmacologic and, especially, invasive treatment varies widely in different hospitals. These results underline the importance of correct initial risk stratification and uniform treatment following the recommendations of clinical guidelines.

Key words: *Acute coronary syndromes. Unstable angina. Prognosis. Treatment. Registry. Variability.*

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Perfil clínico, pronóstico y variabilidad en el tratamiento del síndrome coronario agudo sin elevación del segmento ST. Datos del registro PEPA

Objetivos. Conocer el perfil clínico y la variabilidad interhospitalaria en el tratamiento y pronóstico de los pacientes con síndrome coronario agudo sin elevación del segmento ST.

Pacientes y método. Se analizaron los datos del estudio PEPA, registro prospectivo que incluyó a 4.115 pacientes ingresados en 18 hospitales españoles.

Resultados. La edad media fue de 65 años, un 33% eran mujeres y un 26%, diabéticos. Se observaron grandes diferencias en el tipo de pacientes ingresados en cada centro, especialmente en los antecedentes patológicos, revascularización coronaria previa y comorbilidad. El 93% de los pacientes recibieron tratamiento antiagregante, el 45%, heparina, el 42%, bloqueadores beta, el 67%, nitratos y el 46%, antagonistas del calcio. Durante el ingreso se realizó una ergometría al 37% de los pacientes, coronariografía al 32%, angioplastia coronaria al 9% y cirugía de revascularización al 4%. La variabilidad fue mínima en la administración de antiagregantes plaquetarios, importante en la de heparina y bloqueadores beta, y muy marcada en el uso de procedimientos de revascularización. La mortalidad y la incidencia de muerte o infarto fue del 2,6 y 4,4% durante la hospitalización, y del 4,6 y 8% a

ABBREVIATIONS

CV: coefficient of variation.
AMI: acute myocardial infarction.
ACEI: angiotensin converting enzyme inhibitors.
ACS: acute coronary síndrome.
NSSACS: non-ST segment acute coronary síndrome.

los 3 meses, con una amplia variabilidad interhospitalaria. Estas diferencias dejaron de ser significativas tras ajustar por las características clínicas y el tratamiento recibido en el momento del ingreso.

Conclusiones. Los pacientes con síndrome coronario agudo sin elevación del segmento ST forman un grupo heterogéneo con una elevada incidencia de complicaciones y con una gran variabilidad interhospitalaria en su manejo terapéutico, tanto farmacológico como, sobre todo, invasivo. Estos resultados resaltan la importancia de la correcta estratificación inicial del riesgo y la homogeneización de su tratamiento, siguiendo las recomendaciones de las guías de práctica clínica.

Palabras clave: *Síndrome coronario agudo. Angina inestable. Pronóstico. Tratamiento. Registro. Variabilidad.*

INTRODUCTION

The information available on the characteristics, treatment, and prognosis of patients with acute coronary syndrome (ACS) comes from data obtained from clinical studies and, especially, from randomized clinical trials that tend to include patients who are selected with a risk profile lower than that of the general population.[1] Thus, clinical practice records contain important information regarding the management and prognosis of these patients.

The treatment of patients with ACS and ST segment elevation varies considerably among countries and hospitals,[2-7] which points out the existence of significant differences in healthcare technology, the level of knowledge of physicians with regard to the best treatment available, and their perception of the risk to benefit ratio, as well as the particular characteristics of each hospital. On the other hand, various studies have shown that this variability may also translate into significant differences in mortality rates.[6-9]

Information is scarce as to whether this variability in the management and prognosis also occurs in the case of patients with non-ST segment acute coronary syndromes (NSSACS). The aim of our study was to analyze the heterogeneity in the clinical profile and the level of variability in the treatment and prognosis of patients with NSSACS in Spanish hospitals. To this end, we analyzed the data obtained from the PEPA

study (Proyecto de Estudio del Pronóstico de la Angina) (Project for the Study of Prognosis in Angina), a prospective observational study designed to evaluate the prognosis of patients with suspected NS-SACS from the data available at the time of admission.[10]

PATIENTS AND METHODS

Patients

The PEPA registry was a multicenter prospective study which included all patients with suspected NS-SACS seen consecutively in the emergency department of 18 Spanish medical centers. The methodology and results of the study were published previously.[10,11] In summary, in order to achieve homogeneity in the treatment of patients, medical centers with a hemodynamic laboratory available were invited to participate. The study included patients who went to the hospital due to chest pain or discomfort, which was considered by a cardiologist to probably be ischemic in origin after an initial evaluation performed within the first 12 hours following admission. Those patients with persistent ST segment elevation and those who had been transferred from other hospitals for diagnostic evaluation or treatment were excluded from the study.

Clinical and electrocardiographic data

All the clinical and electrocardiographic definitions are detailed in a protocol that was available to all physicians in the emergency rooms of the participating hospitals. The baseline patient characteristics were noted in the emergency department, within 12 hours following admission, on specially designed forms. Clinical information with regard to demographic data, cardiovascular risk factors, cardiovascular and non-cardiovascular co-morbidity, previous treatment, clinical presentation, and ECG findings were collected upon admission.

The final diagnosis was established with the information obtained during the hospital stay and included one of the following categories: acute myocardial infarct (AMI) with q-wave, non-Q-wave AMI, unstable angina, or non-specific chest pain. The diagnosis of AMI was made when an increase in creatinkinase (CK) of more than double the normal limit was observed, in conjunction with an increase in the MB isoforms (MB-CK). Telephone followup was carried out at 1 month and 3 months, and at that time information regarding their vital state was obtained from 94% of the patients in the study.

Quality control of the data was performed by an independent clinical trials monitoring company (Verum Itempharma), which verified in the database of each hospital the admission of all patients included in the

TABLE 1. Baseline characteristics of the patients studied: mean values of the population studied and interhospital differences

	No. (%)	Differences between hospitals	
		Interval	CV
Age 65±11 years			
Sex: women	1354 (33)	20%-39%	17%
Coronary risk factors			
Diabetes mellitus	1057 (26)	16%-35%	20%
Arterial hypertension	2181 (53)	23%-62%	17%
Hypercholesterolemia	1598 (39)	27%-52%	18%
Family history of early ischemic cardiopathy	576 (14)	7%-38%	49%
Smoking			
No	1954 (48)		
Ex-smoker	1147 (28)		
Smoker	990 (24)	15%-33%	20%
History of ischemic cardiopathy			
Angina	1624 (40)	24%-57%	23%
Angina requiring admission	1150 (29)		
Myocardial infarct	1369 (33)	26%-41%	14%
Coronary angioplasty	370(9)	3%-15%	49%
Heart surgery	305 (7)	2%-19%	57%
Peripheral vascular disease	499 (12)	3%-23%	49%
Cerebrovascular accident	249 (6)	2%-12%	47%
Renal insufficiency (creatinine ≥2)	68 (2)	0%-4%	74%

CV indicates coefficient of variation between hospitals.

study and analyzed the clinical history of those who suffered an adverse event during the followup period. In addition, the company verified the veracity of the data from a random sample of 10% of the population who did not experience an event.

Statistical analysis

Quantitative variables were expressed as means and standard deviations or averages and interquartile intervals if they did not follow normal distribution, and qualitative variables were expressed as numbers and percentages. To describe heterogeneity in the clinical profile of the patients and the degree of interhospital variability in the use of drugs, diagnostic and therapeutic procedures, as well as the prognosis of the patients, the coefficient of variation (CV) was calculated —(standard deviation/mean)×100—. A variability of less than 10% was considered clinically acceptable, significant when it was between 10% and 25%, and excessive when it was greater than 25%. The prognosis at 3 months (death or AMI) was analyzed via Kaplan-Meier survival curves, which were compared via the log-rank test. The differences between hospitals were analyzed via the Cox proportional hazards regression model after adjustment for the variables available at the time of admission which in previous analysis had been shown to have an independent predictive value. These were: age greater than 65 years, diabetes, peripheral

valve disease, previous neoplasm, post-infarct angina, 2 or more angina crises during the 24 hours prior to admission, heart failure (Killip class ≥2), ST segment decline on ECG performed at the time of admission, and elevation of the markers for necrosis.[10] Data analysis was performed via the SAS statistical package.

RESULTS

During the study period a total of 4115 patients were included from the 18 participating hospitals. The diagnosis reached at the end of the hospitalization period was q-wave AMI in 75 patients (1.8%), non-Q-wave AMI in 393 patients (9.6%), unstable angina in 2987 patients (72.6%), and non-coronary or indeterminate pain in 660 patients (16%). Twenty-six percent of patients were admitted to the coronary care unit, 53% of patients were admitted to the cardiology unit, 9% of patients were admitted to the internal medicine unit, and 12% of patients were discharged from the emergency room.

Clinical characteristics

Baseline characteristics of the patients are described in Table 1. The mean patient age was 65 years ±11 years, 33% were women, 26% had diabetes, and 33% had a history of infarct. Of note, 40% of the patients

TABLE 2. **Form of clinical presentation and data obtained on admission: mean values of the population studied and interhospital differences**

	No. (%)	Differences between hospitals	
		Interval	CV
Typical coronary pain	3626 (88)	65%-97%	60%
>2 episodes of pain during the past 24 h	740 (19)		
Killip class ≥ 2	383 (9)	3%-14%	37%
ECG on admission			
Normal	1550 (38)		
Negative T waves	817 (20)	14%-35%	30%
ST segment decline or elevation	1748 (42)	19%-60%	23%
Atrial fibrillation	242 (6)	0%-8%	42%
CK-MB elevation	393 (10)	4%-23%	52%

CK-B indicates MB creatinkinase fraction; CV, coefficient of variation between hospitals.

had a history of angina and 29% had been admitted previously for this reason.

There were notable differences in the type of patients admitted to each hospital, especially in the proportion of women and diabetics, with interhospital CVs of 17% and 20%, respectively. The same was the case with patients with a history of cardiovascular disease, particularly in the case of differences recorded in the prevalence of renal insufficiency, peripheral vascular disease, and previous cerebrovascular accident, with CVs of 79%, 49%, and 47%, respectively, as well as a history of angioplasty and heart surgery (Table 1).

At the time of admission, 88% of patients presented with typical coronary pain; in 56% of cases the pain lasted more than 20 minutes and in 80% of cases the pain occurred at rest during the 48 hours prior to admission. Nine percent of patients had signs of heart failure, 62% of patients had a pathological ECG, especially due to transitory ST segment elevation or decli-
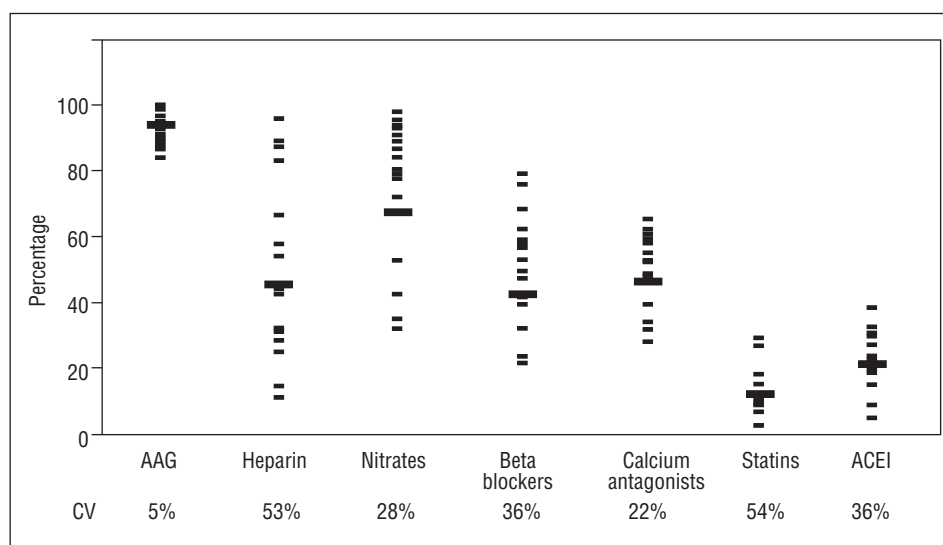
ne (42%), and 10% of patients had an increase in CK-MB. The greatest differences between the participating hospitals were observed in the qualification of the type of pain, the existence of heart failure, the presence of atrial fibrillation, and elevation of CK-MB (Table 2).

Treatment

Ninety-three percent of patients received antiaggregate treatment, 45% of patients received anticoagulant treatment, 42% of patients received betablockers, 67% of patients received nitrates, 46% of patients received calcium antagonists, 6% of patients received statins, and 20% of patients received angiotensin converting enzyme inhibitors (ACEI). Of note, the smallest variability was in the use of anti-aggregants, with a CV of 5%, and the greatest variability was in the use of heparin, beta blockers, statins, and ACEI, with a CV of more than 35% (Figure 1).

The average hospital stay was 8 days (range 4 to 13

Fig. 1. Pharmacological treatment during admission. Of note is the minimal interhospital variability in the administration of platelet anti-aggregants and the great variability in the administration of the other drugs. AAG indicates platelet anti-aggregants; CV, variation coefficient; ACEI, angiotensin converting enzyme inhibitors.
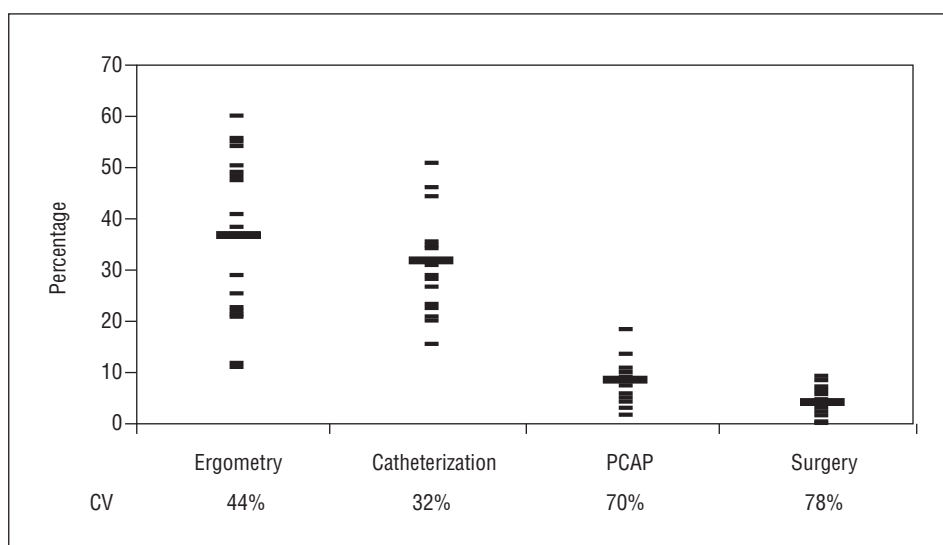
Fig. 2.. Diagnostic and therapeutic procedures carried out during hospitalization. Interhospital variability in the use of invasive procedures was considerable, especially in the case of coronary revascularization. PCAP indicates percutaneous coronary angioplasty; CV, coefficient of variation. This study was carried out in part with the investigative assistance of Pfizer Laboratories.

days) with an interhospital interval of 6 to 11 days. The majority of the diagnostic procedures were performed during this period, with stress tests being performed in 37% of patients and coronary angiography in 32% of patients (Table 3). Only 13% of patients underwent revascularization before discharge, whether via angioplasty (8.7% of patients) or surgery (4.3% of patients). Nevertheless, at 3 months 22% of patients had undergone revascularization. There was great variability in the use of diagnostic procedures during hospitalization, with a CV of 44% for performance of a stress test and 32% for coronary angiography, and enormous variability in the use of revascularization procedures (Figure 2).

Patient course

The nosocomial mortality rate was 2.6% and the incidence of death or infarct was 4.4%. At 3-month followup, the incidence rate for these complications was 4.6% and 8%, respectively (Table 3), with a wide range of interhospital variability (Figure 3). After adjustment for other clinical variables, the multivariate analysis did not show the admitting hospital to be a variable associated with prognosis, either in the case of mortality ($P=.20$) or the combined incidence of mortality or infarct ($P=.17$). The results also did not change when adjusted, also, for the type of treatment received ($P=.43$ and $P=.21$, respectively).

DISCUSSION

The PEPA study is the first Spanish registry of patients selected who did not have NSSACS, performed on a broad sample of patients admitted to hospitals with a varied geographic distribution. This stu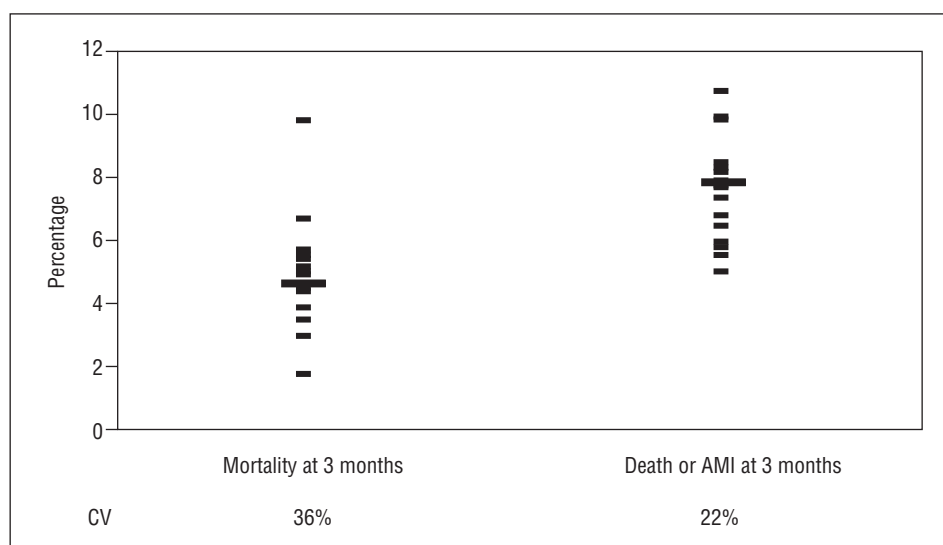dy shows, once again, the heterogeneity of the clinical profile of patients with this disease and supports the fact that great variability exists between different Spanish hospitals in their medical treatment, use of diagnostic tests, and, particularly, in revascularization procedures with regard to these patients.

There are multiple registries of the treatment and prognosis of patients with myocardial infarction,[2-7] but there are few that have studied patients with NSSACS. In Spain, the only registry published up to the present time is the RESCATE registry, carried out between 1992 and 1994 in 4 Catalonian hospitals that included 830 patients who had been admitted with the certain diagnosis of unstable angina.[12] In that study, patients were excluded who had a history of myocardial infarct, revascularization surgery, coronary angiography, or angioplasty during the 6 months prior to admission, as were those patients with CK-MB elevation, making comparison of their results difficult. In 5 international registries the characteristics and the clinical course of patients with NSSACS have been analyzed,[13-17] and these studies serve as a reference point for comparison with our study.

Patient heterogeneity

Only 2% of the patients in our study were finally diagnosed with Q-wave infarct and 10% with non-Q-wave infarct, in comparison with 9% and 31%, respectively, in the Euro Heart Survey.[17] In the GRACE registry, 6% of patients were diagnosed with an infarct with ST segment elevation and 24% of patients with an infarct without ST segment elevation.[16] These differences are probably due to different inclusion criteria, as our study included patients seen in the emergency room with suspected NSSACS, while the ENACT registry,[15] GRACE registry,[16] and Euro Heart Survey[17] included patients with a certain diagnosis of ACS who

Fig. 3. Prognosis at 90 days for the patients studied. Great inter-hospital variability can be seen in the prognosis of these patients, both with regard to mortality and the incidence of death or myocardial infarct. AMI indicates acute myocardial infarct; CV, coefficient of variation.

were admitted to coronary care units or cardiology units, including even those who had been transferred from other hospitals. In addition, the development of the diagnostic criteria of an infarct over recent years with the decrease in the CK-MB elevation threshold and, especially, the introduction of troponin measurement, has increased the percentage of infarcts diagnosed.

The average length of hospital stay of our patients was increased, although it was similar to that found in other recent registries[15,17] and with marked intra- and interhospital differences. Initial risk stratification, in the emergency room, should allow notable shortening of the length of hospital stay for these patients. On the other hand, only a fourth of the patients were admitted to a coronary care unit, in contrast with other registries where half of the patients were,[17] which reflects the lesser accessibility of these units to patients with NS-SACS in Spain.[18]

The differences found between the various hospitals

are The mean age, percentage of women, risk factors, and ECG changes were similar to those found in other studies.[12-17,19] In contrast, the percentage of patients with a history of AMI and pathological ECG results on admission was greater in the OASIS[13] and PRAIS-UK[14] registries, with regard to the distinct inclusion criteria of these registries which required the presence of a history of ischemic cardiopathy or ECG changes at the time of admission. It is interesting to note that, in our study, nearly one-third of patients had been admitted previously for the same reason, which shows the high recurrence rate of NSSACS and the significant healthcare burden involved.

The differences found between the various hospitals are notable with regard to demographic characteristics, pathological history, and patient co-morbidity, especially in the percentage of women and diabetics, patients with a history of coronary revascularization, and the existence of peripheral valvulopathy, heart failure, or renal insufficiency. These data confirm the known

TABLE 3. **Hospital course and followup 3 months later**

	Hospitalization n (%)	3 month followup* n (%)
Average duration of hospital stay, days	8 (4-13)	
Tests performed		
Ergometry	1522 (37)	1545 (38)
Coronary angiography	1308 (32)	1545 (38)
Angioplasty/stent	359 (9)	539 (13)
Heart surgery	179 (4)	355 (9)
Course		
Death	106 (2.6)	189 (4.6)
Myocardial infarct	109 (2.6)	185 (4.5)
Death or infarct	182 (4.4)	325 (8)

*Including the hospitalization period.

heterogeneity of patients with NSSACS, underline the difficulty in extrapolating results obtained locally, and emphasize the importance of correct initial risk stratification.[20-22]

Variability in treatment

In our study we observed the appropriate use of aspirin, greater than that observed in other registries, especially those performed in the United Kingdom, in which it was used in 87% to 89% of cases.[14-15] On the other hand, there was a low rate of beta blockers use (42%) and heparin use (45%), drugs whose efficacy in these patients was demonstrated many years ago. In comparison, beta blockers were used in 74% of patients in the GRACE study[16] and heparin was used in 72% in the registries contemporary with our study: OASIS[13] and PRAIS-UK.[14] The inclusion in our study of patients with suspected NSSACS, with or without ECG changes or CK-MB elevation, may explain part of these differences.

One of the most notable aspects of our study was the low use of invasive procedures, in both the diagnostic and therapeutic sense, during hospitalization with regard to the inclusion of patients with suspected but not certain NSSACS. Even so, the numbers were greater than in the PRAIS-UK study,[14] in which the use of coronary angiography, angioplasty, and surgery was minimal (10%, 4%, and 2%, respectively), reflecting the infrequent use of these procedures in the United Kingdom, data which is also corroborated by the ENACT study.[15] In contrast, in later international registries, the percentage of patients who underwent coronary angiography and percutaneous revascularization was clearly higher (52% and 25% of patients, respectively, in the Euro-Heart[17] study and 45% and 21% of patients, respectively, in the GRACE study[16]), in agreement with the later recommendations of clinical practice guidelines and recent studies that have shown the efficacy of an initial invasive strategy in patients with NSSACS and at moderate to high risk.[20-22]

In any case, in our study, greater variability in the management of patients was seen in the use of coronary revascularization procedures, with variation coefficients of more than 70%. Both the low use of invasive procedures and the enormous variability in their use are even more surprising if we take into account the fact that all the participating hospitals had a hemodynamic laboratory, and therefore the variability must be attributed to the broad differences in criteria that exist for the indication for coronary angiography.

Prognosis

The incidence rate of complications during hospitalization was low. Nevertheless, after hospital discharge, the number of events was the same as that seen during hospitalization. At 3 months, the overall mortality rate was 4.5%, and the mortality or infarct rate was 8%, results that are similar to those reported in other studies.[13,14,16,17,23]

As in the case of treatment, the patient prognosis was very different from one hospital to another, with mortality rates at 3 months that varied from 2% to 10% of patients. Nevertheless, when these numbers are adjusted for clinical characteristics and the treatment begun at the time of admission, the differences decrease and cease to be statistically significant. This confirms, once again, the heterogeneity of the patients included in the study with the diagnosis of NSSACS and the difficulty in establishing comparisons between the treatment and prognosis for different patients groups without analyzing their risk profiles.

STUDY LIMITATIONS

Medical and, above all, invasive treatment has changed over the past years in response to the results obtained from randomized studies and the publication of various clinical practice guidelines. On the other hand, important prognostic markers, such as the troponins, were not available previously and their measurement may help diminish the variability in treatment of these patients.[20-22,24] Registries underway at present will provide proof of whether this is the case or not. It is unlikely, nevertheless, that the clinical profile of patients has changed, given the known heterogeneity of this syndrome. Finally, our study was performed in hospitals that had a hemodynamic laboratory available, so that our results cannot be extrapolated to regional hospitals, which tend to treat low-risk patients.

CLINICAL IMPLICATIONS

The PEPA registry provides important information regarding the clinical characteristics and management of patients with acute coronary syndromes without ST segment elevation in Spanish hospitals, underlining the great heterogeneity of patients and the great interhospital variability in their therapeutic management both pharmacologically and, above all, with regard to the use of invasive procedures. This points out the importance of initial risk stratification of these patients at the time of their admission to the emergency room and that the homogenization of their treatment needs to follow the recommendations of clinical practice guidelines.

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