Spanish Acute Aortic Syndrome Study (RESA). Better Diagnosis Is Not Reflected in Reduced Mortality

Arturo Evangelista, a Ferran Padilla,b Jordi López-Ayerbo,c Francisco Calvo,d José Manuel López-Pérez,e Violeta Sánchez,f César Morís,g Rubén Fernández-Tarrio,h José A. San Román,i Daniel Saura,j Francisco Nistal,k Josep M. Alegret,l Pastora Gallego,m and Rio Aguilar,a on behalf of the hospitals participating in the Spanish Acute Aortic Syndrome Study*

aServicio de Cardiología, Hospital Vall d’Hebron, Barcelona, Spain
bServicio de Cardiología, Hospital de Bellvitge, L’Hospitalet de Llobregat, Barcelona, Spain
cServicio de Cardiología, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain
dServicio de Cardiología, Hospital do Meixoeiro, Vigo, Pontevedra, Spain
eUnidad de Cuidados Intensivos, Hospital Juan Canalejo, A Coruña, Spain
fServicio de Cardiología, Hospital 12 de Octubre, Madrid, Spain
gHospital Central de Asturias, Oviedo, Asturias, Spain
hServicio de Cirugía Cardiaca, Hospital Son Dureta, Palma de Mallorca, Islas Baleares, Spain
iServicio de Cardiología, Hospital Clínico de Valladolid, Valladolid, Spain
jServicio de Cardiología, Hospital Virgen de la Arrixaca, Murcia, Spain
kServicio de Cirugía Cardiaca, Hospital Valdecilla, Santander, Cantabria, Spain
lHospital de la Santa Creu i Sant Pau, Barcelona, Spain
mServicio de Cardiología, Hospital Virgen de la Macarena, Sevilla, Spain

Introduction and objectives. Because acute aortic syndrome (AAS) is associated with high mortality, early diagnosis and treatment are vital. The aim of the Spanish Acute Aortic Syndrome Study (RESA) was to investigate the effectiveness of current treatment of AAS in a broad range of tertiary care hospitals in Spain.

Methods. Between January 2005 and December 2007, 24 tertiary care hospitals reported data on 519 patients with AAS (78% male; mean age, 61 [13] years; range, 20-92 years): 357 had type A AAS and 162 had type B.

Results. The time delay between symptom onset and diagnosis was <24 hours in 67% of cases and >72 hours in 11%. Some 80% of patients with type A AAS were treated surgically. The interval between diagnosis and surgery was <24 hours in 90% of cases. In patients with type B AAS, 34% received invasive treatment: 11% had surgery and 23% underwent endovascular procedures. Mortality during hospitalization in patients with type A disease was 33% in those treated surgically and 71% in those treated medically. Mortality in patients with type B disease was 17% with medical treatment, 27% with endovascular treatment, and 50% with surgical treatment.

Conclusions. Despite significant advances in the diagnosis of AAS, in-hospital mortality remains high. The findings of this study are representative of a broad range of unselected patients undergoing treatment for the disease and support the need for continuing improvements in therapeutic approaches to AAS.

Key words: Acute aortic syndrome. Aortic dissection. Mortality. Heart surgery.

Registro Español del Síndrome Aórtico Agudo (RESA). La mejora en el diagnóstico no se refleja en la reducción de la mortalidad

Introducción y objetivos. El síndrome aórtico agudo (SAA) tiene una alta mortalidad que obliga a un diagnóstico y un tratamiento precoz. El Registro Español del Síndrome Aórtico Agudo (RESA) pretende valorar los resultados actuales en el manejo del SAA en una amplia cohorte de hospitales terciarios de nuestro país.

Métodos. Desde enero de 2005 hasta diciembre de 2007, 24 hospitales terciarios incluyeron a 519 pacientes con SAA (el 78% varones; media de edad, 61 ± 13 [intervalo, 20-92] años), 357 de tipo A y 162 de tipo B.

Resultados. El intervalo entre los síntomas y el diagnóstico fue < 24 h en el 67% de los casos y > 72 h en el 11%. El 80% de los SAA de tipo A fueron tratados quirúrgicamente. El intervalo entre el diagnóstico y la cirugía fue < 24 h en el 90% de los casos. En el SAA tipo B recibieron tratamiento invasivo el 34%; cirugía, el 11% y tratamiento endovascular, el 23%. La mortalidad del tipo A durante la hospitalización fue el 33% de los tratados
Evangelista A et al. Spanish Acute Aortic Syndrome Study

INTRODUCCIÓN

Acute aortic syndrome (AAS) is an acute process affecting the aortic wall that is associated with high rates of morbidity and mortality. Essentially, it involves three entities: aortic dissection, intramural hematoma, and penetrating ulcer.1 The incidence of AAS is approximately 20 to 40 cases per million population per year,2,3 80% of which are dissections, 15% are intramural hematomas, and 5% are penetrating ulcers. The advances in imaging techniques, combined with the progress in surgical and endovascular techniques, have modified the diagnosis and treatment of this syndrome in recent years.4-9 A number of studies have reported updated information on the diagnosis, treatment, and prognosis of this condition.10-18 Nevertheless, the majority of them present data obtained from a single center, with retrospective series documented over many years that do not reflect the current reality in the management of this entity.13-16 On the other hand, other multicenter studies are biased due to the inclusion of patients from centers of excellence,10-12 a circumstance that does not allow the extrapolation of the results to the health care field in general.

The objective of the Spanish Acute Aortic Syndrome Study (RESA) was to analyze the diagnosis, treatment, and mortality of AAS in Spain with the aim of achieving possible improvements in its management.

MÉTODOS

The authors carried out a prospective, descriptive, and observational study in tertiary centers capable of carrying out imaging and hemodynamic techniques and heart surgery 24 hours a day. Twenty-four of the 34 tertiary hospitals proposed agreed to participate in the Spanish Acute Aortic Syndrome Study. The participating centers accepted the commitment to include all the patients with AAS evaluated prospectively and consecutively, regardless of whether they had been referred from other centers or had been diagnosed in their own hospital. The recruitment period was from January 2005 to December 2006. In all, 519 patients with AAS were included. 349 with involvement of ascending aorta (type A) and 170 (32.7%) with involvement of only descending aorta (type B). In 430 cases (82.9%), the diagnosis was aortic dissection (312 type A and 118 type B), in 72 (13.9%), it was intramural hematoma (32 type A and 40 type B), and in 17, it was penetrating ulcer (5 type A and 12 type B). In 8 patients with type B aortic dissection, there was retrograde extension of the dissection into the uppermost part of the ascending aorta during the initial days of the hospital stay; thus, in the end, 357 AAS were considered to be type A and 162, type B. In all, 47.6% of the patients had been referred from regional hospitals or other centers in which heart surgery was not performed.

Data Collection

The Cardiology and Cardiac Surgery Departments of each hospital were asked to participate both in the collection and validation of data, and to choose a single coordinator for each center who would transmit the information. The patients were identified in the emergency service, imaging departments and on the basis of hospital discharge records. The diagnosis was based on clinical data, information from imaging techniques, intraoperative findings and/or postmortem examination. The data collection form included 140 variables with demographic information, medical record, physical examination, imaging techniques, treatment, mortality, and in-hospital complications. The variables were defined in agreement with the International Registry of Acute Aortic Dissection (IRAD)10 in order to facilitate a possible future comparison. The IRAD is an international registry that was created in 1996 with the participation of different European countries, the United States, and Japan. A history of arteriosclerosis was considered if the patient had had a previous diagnosis of ischemic heart disease, obliterator arteriopathy or stroke. A systolic arterial pressure <80mmHg was considered to indicate the presence of shock, and a creatinine level >1.5 mg/100 mL was indicative of abnormal renal function. The participants were instructed to include every case, providing the available data, even if there was little information. Any doubts
Symptoms, Signs on Examination, and Supplementary Tests

Chest pain was the most common presenting symptom (95.9%). In type A AAS, the pain was more frequently localized to the anterior chest than in type B (70.8% vs 43.8%; \( P < .001 \)), and in type B AAS, it was more frequently localized to the back (33.9% vs 56.8%; \( P < .001 \)) or to the abdomen (19.6% vs 28.4%; \( P < .03 \)). Both syncope and neurological deficit were more common presenting symptoms in type A AAS (18.2% and 11.88%, respectively) (Table 2). Hypertension during the acute phase occurred more frequently in type B AAS (31.3% vs 63%; \( P < .001 \)). In contrast, hypotension/shock and congestive heart failure were more common in type A AAS.

The chest x-ray was strictly normal in 16.6% of the cases. Mediastinal widening was observed more frequently in type A AAS (57.7% vs 43.2%; \( P < .001 \)) and the incidence of pleural effusion was higher in type B AAS (5.9% vs 13%; \( P = .006 \)). The electrocardiogram was normal in 37.6% of the patients, and reversible changes in repolarization indicative of ischemia/injury were found in 13.1% of the cases (Table 2).

### Data Analysis

The data were analyzed using the SPSS 13 statistical software package. The quantitative variables were expressed as the mean (standard deviation) and the qualitative variables as the percentage. For the intergroup comparison of the quantitative variables, Student \( t \) test was employed, and the \( \chi^2 \) test was used to compare the qualitative variables. A \( P \) value less than .05 was considered to indicate statistical significance.

### RESULTS

#### Demographic Data

The study included 519 patients with AAS, 402 men (77.4%) and 117 women (22.5%), with a mean age of 61 (13) years (range, 20-92 years). The demographic data and history of cardiovascular disease are shown in Table 1. The patients with type B AAS exhibited a higher incidence of cardiovascular risk factors such as hypertension (67.5% vs 79%; \( P = .009 \)), smoking (41.5% vs 52.5%; \( P = .02 \)), dyslipidemia (19.9% vs 27.8%; \( P = .05 \)), or a history of arteriosclerotic disease (14% vs 29%; \( P < .001 \)). In contrast, those with type A AAS showed a higher incidence of Marfan’s syndrome (8.1% vs 2.5%; \( P < .01 \)) and aortic valve disease (11.5% vs 3.1%; \( P < .001 \)).

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**TABLE 1. Demographic Data and History of Disease in Patients With Acute Aortic Syndrome**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n=519)</th>
<th>Type A (n=357)</th>
<th>Type B (n=162)</th>
<th>( P^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>60.9 (13.3)</td>
<td>60.3 (0.7)</td>
<td>62.3 (1.0)</td>
<td>.10</td>
</tr>
<tr>
<td>Age &gt;70 years, n (%)</td>
<td>154 (29.7)</td>
<td>92 (25.7)</td>
<td>62 (36.4)</td>
<td>.01</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>402 (77.5)</td>
<td>268 (75.1)</td>
<td>134 (82.7)</td>
<td>.06</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>369 (71.1)</td>
<td>241 (67.5)</td>
<td>128 (79.0)</td>
<td>.009</td>
</tr>
<tr>
<td>Smoking habit, n (%)</td>
<td>233 (44.9)</td>
<td>148 (41.5)</td>
<td>85 (52.5)</td>
<td>.02</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>116 (22.4)</td>
<td>71 (19.9)</td>
<td>45 (27.8)</td>
<td>.05</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>43 (8.3)</td>
<td>30 (8.4)</td>
<td>13 (8.0)</td>
<td>.90</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>44 (8.5)</td>
<td>28 (7.8)</td>
<td>16 (9.9)</td>
<td>.49</td>
</tr>
<tr>
<td>Arteriosclerosis, n (%)</td>
<td>97 (19.7)</td>
<td>50 (14.0)</td>
<td>47 (29.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Marfan’s syndrome, n (%)</td>
<td>33 (6.4)</td>
<td>29 (8.1)</td>
<td>4 (2.5)</td>
<td>.02</td>
</tr>
<tr>
<td>Aortic aneurysm, n (%)</td>
<td>89 (17.1)</td>
<td>60 (16.8)</td>
<td>29 (17.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Aortic valve disease, n (%)</td>
<td>46 (8.9)</td>
<td>41 (11.5)</td>
<td>5 (3.1)</td>
<td>.44</td>
</tr>
<tr>
<td>Cardiac surgery, n (%)</td>
<td>34 (6.6)</td>
<td>26 (7.3)</td>
<td>8 (4.9)</td>
<td>.10</td>
</tr>
<tr>
<td>Previous dissection, n (%)</td>
<td>20 (4.0)</td>
<td>7 (1.9)</td>
<td>16 (9.8)</td>
<td>.001</td>
</tr>
</tbody>
</table>

SD indicates standard deviation.

\( ^a \)Type A versus type B.

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were resolved by phoning the person responsible in each hospital. Fourteen cases involving chronic, post-traumatic, or iatrogenic aortic conditions were not included in the study.

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**Symptoms, Signs on Examination, and Supplementary Tests**

Chest pain was the most common presenting symptom (95.9%). In type A AAS, the pain was more frequently localized to the anterior chest than in type B (70.8% vs 43.8%; \( P < .001 \)), and in type B AAS, it was more frequently localized to the back (33.9% vs 56.8%; \( P < .001 \)) or to the abdomen (19.6% vs 28.4%; \( P < .03 \)). Both syncope and neurological deficit were more common presenting symptoms in type A AAS (18.2% and 11.88%, respectively) (Table 2). Hypertension during the acute phase occurred more frequently in type B AAS (31.3% vs 63%; \( P < .001 \)). In contrast, hypotension/shock and congestive heart failure were more common in type A AAS. The chest x-ray was strictly normal in 16.6% of the cases. Mediastinal widening was observed more frequently in type A AAS (57.7% vs 43.2%; \( P = .002 \)) and the incidence of pleural effusion was higher in type B AAS (5.9% vs 13%; \( P = .006 \)). The electrocardiogram was normal in 37.6% of the patients, and reversible changes in repolarization indicative of ischemia/injury were found in 13.1% of the cases (Table 2).

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**Diagnosis Using Imaging Techniques**

Computed tomography was the first technique to be employed in 77.1% of the patients, transesophageal echocardiography in 18.7%, aortography in 2.9%, and magnetic resonance in 0.4%. More than 1 imaging technique was utilized in 53.2% of the
Surgical treatment was performed in 284 (79.6%) of the 357 patients with type A AAS. In 20.4% of the patients who did not undergo surgical treatment, it was due to advanced age (>75 years) in 17 (4.8%), to comorbidity in 8 (2.2%), to stable intramural hematoma in 6 (1.7%), to refusal on the part of the patient in 8 (2.2%), and to death prior to being accepted for surgery in 25 (7%). The time elapsed between the diagnosis and surgery was <24 hours in 90% of the cases (median, 4 hours; P25-P75, 3-7 hours). Among the patients with type B AAS, the treatment was medical in 107 cases (66.0%), endovascular in 37 (22.8%), and surgical in 18 (11.1%). The need for endovascular or surgical treatment was due to persistent pain in 15 cases, extension of the dissection in 2, uncontrolled hypertension in 6, imminent aortic rupture in 58.5% of those of type A AAS and 46.2% of those of type B AAS. The time elapsed between the onset of symptoms and the diagnosis was <24 hours in 70.3% of the cases (median, 5 hours; 25th-75th percentiles [P25-P75], 3-10 hours); the interval was <72 hours in 18.7% of the patients and >72 hours in 11%.

Acute Complications

Pericardial effusion was diagnosed in 37.3% of the cases of type A and cardiac tamponade in 16.2%; the incidence of periaortic hematoma was the same in both type A and type B (24.4% vs 25.9%) in type B AAS; no significant difference. There were no significant differences between the 2 types of AAS in terms of the incidence of peripheral ischemia (10.1% vs 6.2%) or mesenteric ischemia (6.4% vs 6.2%).

### Treatment

Surgical treatment was performed in 284 (79.6%) of the 357 patients with type A AAS. In 20.4% of the patients who did not undergo surgical treatment, it was due to advanced age (>75 years) in 17 (4.8%), to comorbidity in 8 (2.2%), to stable intramural hematoma in 6 (1.7%), to refusal on the part of the patient in 8 (2.2%), and to death prior to being accepted for surgery in 25 (7%). The time elapsed between the diagnosis and surgery was <24 hours in 90% of the cases (median, 4 hours; P25-P75, 3-7 hours). Among the patients with type B AAS, the treatment was medical in 107 cases (66.0%), endovascular in 37 (22.8%), and surgical in 18 (11.1%). The need for endovascular or surgical treatment was due to persistent pain in 15 cases, extension of the dissection in 2, uncontrolled hypertension in 6, imminent aortic rupture in 9,
DISCUSSION

The results of the present study demonstrate an important advance in the diagnosis of AAS, as more than 70% of the cases were diagnosed within the first 24 hours after the onset of the symptoms. However, the total mortality is as high in type A as in type B, a circumstance that indicates the need to optimize the therapeutic management.

It has classically been accepted that the mortality rate associated with AAS is higher than 1% per hour if proper treatment is not initiated rapidly.19,20 To improve the prognosis of these patients, a high clinical suspicion, in the presence of clinical signs or symptoms suggestive of AAS, is essential, especially in hypertensive patients or those with Marfan’s syndrome or arteriosclerotic aneurysms. When AAS is suspected, an imaging technique should be performed as soon as possible to confirm or rule out the diagnosis and initiate treatment immediately.

Different studies have reported the demographic variables, symptoms and signs associated with AAS,10,21 but we have no information from a multicenter study involving a large series of patients in Spain. Comparing the findings with those reported in the IRAD,10 we observe that the population is somewhat younger (60.9 years vs 63.1 years), there is a higher proportion of men (77.5% vs 65.3%) and a lower incidence of patients who had undergone previous heart surgery (6.6% vs 17.9%) (Table 3).

Among the presenting clinical signs and symptoms recorded in the present study, there is a notably higher frequency of syncope (14.3% vs 9.4%) and

organ ischemia in 5, peripheral ischemia in 4, and severe aortic dilation in 6. Three patients required percutaneous fenestration and 3 patients with type A AAS also underwent endovascular treatment in descending aorta.

Mortality

The total in-hospital mortality was 35.4% (184/519) (Table 3). The rate of mortality associated with type A AAS during the hospital stay was 41.1% (147/357), 33.4% (95/284) among those patients treated surgically, and 71.2% (52/73) among those treated medically (P=.002). The total mortality in type B was 22.8% (37/162), being lower among patients who received medical treatment (16.8% [18/107]; P<.05) than among those who underwent endovascular treatment (27.0% [10/37]) or were treated surgically (50.0% [9/18]) (Figure).

TABLE 3. Treatment and Outcome in Patients With Acute Aortic Syndrome (n=519)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Type A (n=357)</th>
<th>Type B (n=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical, n</td>
<td>284</td>
<td>18</td>
</tr>
<tr>
<td>Medical, n</td>
<td>73</td>
<td>107</td>
</tr>
<tr>
<td>Endovascular, n</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical treatment, n (%)</td>
<td>95 (33.4)</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Medical treatment, n (%)</td>
<td>52 (71.2)</td>
<td>18 (16.8)</td>
</tr>
<tr>
<td>Endovascular treatment</td>
<td>10 (27)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Thirty-day mortality in type A and type B acute aortic syndrome according to the treatment received.
of pulse deficit (22.2% vs 15.1%). Classically, an abnormal chest x-ray has been considered to be highly useful in the diagnosis of aortic dissection. However, in agreement with other series, in more than 30% of the cases, it reveals no evidence of mediastinal widening or abnormalities in the aortic contours. Thus, in the study of the causes of acute chest pain, a normal chest x-ray should not rule out the suspicion of AAS. It is not unusual to confuse AAS with acute coronary syndrome, a condition that can result in important complications secondary to thrombolytic treatment. Although the presence of a normal electrocardiogram can increase the suspicion of AAS, our results show that the electrocardiogram is strictly normal in only 38% of the cases, reveals signs of ischemia/injury in 15%, and waveforms indicative of necrosis in 4% of the cases.

One of the major challenges we face in order to improve the diagnosis of AAS is maintaining the necessary degree of clinical suspicion. Some series report that clinicians suspect the diagnosis in less than 50% of the patients with AAS evaluated. A noteworthy finding in the present study is the fact that more than 70% of the cases of AAS were diagnosed within the first 24 hours. This information, which goes unnoticed in the majority of the published series, influences the characteristics of the population included since, the earlier the diagnosis, the poorer the prognosis in the population studied. The choice of the most appropriate imaging technique for the diagnosis of AAS has been widely debated. Some groups consider transesophageal echocardiography to be the technique of choice, but there is growing consensus as to the advisability of performing the available technique with which there is the greatest experience in each center. In the RESA, the use of computed tomography as the first diagnostic technique was more widespread than that reported in the IRAD (77% vs 61%). Notably, in the present series, transesophageal echocardiography was utilized for the initial diagnosis of AAS in only 19% of the cases, versus 33% in the IRAD. Whereas the majority of the IRAD centers are referral centers for aortic disease and have echocardiographers on hand 24 hours a day, this type of tertiary center was not selected for the RESA. In this context, given its availability and the excellent data it provides, computed tomography is the most useful imaging technique for the diagnosis of AAS.

In patients with type A AAS included in the IRAD series, the mean interval between the onset of symptoms and surgical treatment was 79 hours, and between the onset of symptoms and the diagnosis of type B AAS, it was 39 hours. The marked dissemination of knowledge concerning this condition that took place in Spain in recent years has probably led to the fact that the clinical suspicion is high and an imaging technique is rapidly indicated. Another aspect that confirms the improvement in the diagnosis of this disease is reflected by the diagnosis of intramural hematoma in 15% of the cases of AAS, while the rate in the IRAD is only 5%. Our results agree with the majority of the Asian series in which computed tomography is much more frequently employed for the diagnosis of chest pain. Early surgical treatment has been considered essential to improve survival rates in type A AAS. In the present study, the time elapsed between diagnosis and surgical treatment was acceptable, and did not surpass 24 hours in 90% of the cases. However, the mortality rate was high (33%), although not much higher than that obtained in the cross-sectional database recently created in the United States, which included 3013 type A dissections, with a mortality rate of 26%, identical to that reported for the IRAD. The higher mortality of the RESA may be due to the inclusion of more unstable patients.

In the present series, there was a higher incidence of tamponade or shock (18.7% vs 8.4%), of neurological deficit (9.4% vs 4.7%), and of heart failure (10% vs 6.6%) than in the IRAD. The earlier diagnosis, while favorable in terms of patient prognosis, means that more unstable patients are included, who, if their diagnosis had been delayed, would not have reached the hospital and would not have been included in the series. On the other hand, the inclusion of only referral centers with extensive experience in aortic surgery increases the number of patients transferred from other centers, a circumstance that produces a certain bias with respect to inclusion. While in this study, 47% of the patients were transferred from regional hospitals, in the IRAD, this proportion was over 65%. Finally, in the IRAD, 28% of the cases of type A AAS were treated medically, versus 20% in the present series, a fact that suggests that a more selective approach was employed among those patients to be treated surgically in the IRAD centers.

A number of the above mentioned factors could also have played a role in the higher mortality rate among patients with type B AAS since, in the present study, it was 23% and in the IRAD it was 15%. Of the patients with type B AAS in the series we focus on here, 33% required surgical or endovascular treatment, versus 20% in the IRAD. Twenty-three percent of those with type B AAS underwent endovascular treatment because of complications, and the mortality rate was 27%. These results should be considered with caution because of the initial experience of some centers with this therapeutic modality, which can affect both the indication for and the outcome of the treatment.
Taking into account the limitations inherent in all registries, the results of the present study are especially important, as they have been obtained from a large cohort of tertiary hospitals in Spain. All the centers agreed to enroll consecutively all the patients with AAS, and the inclusion of the cases was validated by the cardiology and cardiac surgery departments. The data concerning symptoms, diagnosis, therapeutic management and mortality were completed in every case.

The general information derived from this study may be closer to reality, and contrasts with the results recorded in studies of retrospective series from a single center or in multicenter studies that included only centers of excellence that receive patients transferred from other centers, with a longer delay after the onset of symptoms.

CONCLUSIONS

Despite the important advances in the diagnosis of AAS, the in-hospital mortality remains high. The early diagnosis, the lower number of patients transferred from other centers and the fact that there was no process of selection of the participating hospitals are factors that may have led to the inclusion of more unstable patients with a poorer prognosis. Our results confirm the need to continue the efforts to improve the therapeutic management of AAS. The increased specialization of the surgical teams and the improvement in health care logistics in terms of times to nonelective surgery may help us to achieve this aim. New registries are needed to enable us to assess the changing reality of the management of this disease.

REFERENCES

Evangelista A et al. Spanish Acute Aortic Syndrome Study


APPENDIX 1

Hospital de Bellvitge (L’Hospitalet de Llobregat), Hospital Germans Trias i Pujol (Badalona), Hospital Central de Asturias (Oviedo), Hospital Clínico de Valladolid (Valladolid), Hospital Son Dureta (Palma de Mallorca), Hospital Juan Canalejo (A Coruña), Hospital Virgen Macarena (Sevilla), Hospital Universitario Valdecilla (Santander), Hospital de Sant Pau (Barcelona), Hospital do Meixoeiro (Vigo), Hospital La Paz (Madrid), Hospital Ramón y Cajal (Madrid), Hospital Virgen de la Arrixaca (Murcia), Hospital Clínico (Barcelona), Hospital Carlos Haya (Málaga), Hospital 12 de Octubre (Madrid), Hospital Clínico San Carlos (Madrid), Hospital La Fe (Valencia), Hospital de La Princesa (Madrid), Hospital de Galdakao (Galdakao), Hospital Costa del Sol (Málaga), Hospital Txagorribu (Vitoria), Hospital Universitario de Valencia (Valencia), and Hospital Vall d’Hebron (Barcelona).