

## SPECIAL ARTICLES

# 2002 Update of the Guidelines of the Spanish Society of Cardiology for Unstable Angina/Without ST-Segment Elevation Myocardial Infarction

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Since the Spanish Society of Cardiology Clinical Practice Guidelines on Unstable Angina/Non-Q-Wave Myocardial Infarction were released in 1999, the conclusions of several studies that have been published make it advisable to update current clinical recommendations. The main findings are related to the developing role of Chest Pain Units in the management and early risk stratification of acute coronary syndromes in the emergency department; new information concerning the efficacy of glycoprotein IIb/IIIa inhibitors, clopidogrel and low-molecular-weight heparins in the pharmacological treatment of acute coronary syndromes without ST-segment elevation; and the role of early invasive strategy in improving the prognosis of these patients.

The published evidence is reviewed and the corresponding clinical recommendations for the management of acute coronary syndromes without persistent ST-segment elevation are updated.

**Key words:** *Acute coronary syndromes. Chest pain units. Glycoprotein IIb/IIIa inhibitors. Clopidogrel. Low-molecular-weight heparins. Invasive strategy.*

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## Actualización (2002) de las Guías de Práctica Clínica de la Sociedad Española de Cardiología en angina inestable/infarto sin elevación del segmento ST

Desde la elaboración de las Guías de Práctica Clínica sobre angina inestable/infarto agudo de miocardio sin onda Q de la SEC en 1999, se han publicado numerosos trabajos cuyas conclusiones hacen recomendable modificar las recomendaciones vigentes hasta la fecha. Los hallazgos más importantes están relacionados con el papel emergente de las Unidades de Dolor Torácico en el manejo y la estratificación inicial de los síndromes coronarios agudos en las unidades de urgencias, los nuevos descubrimientos sobre la eficacia de los inhibidores de la glucoproteína IIb/IIIa, el clopidogrel y las heparinas de bajo peso molecular en el tratamiento farmacológico del síndrome coronario agudo sin elevación del segmento ST y el papel de la estrategia invasiva precoz para mejorar el pronóstico de estos pacientes.

En este documento se revisan las evidencias publicadas en estos campos y se actualizan las recomendaciones correspondientes en el manejo de los pacientes con síndrome coronario agudo sin elevación persistente del segmento ST.

**Palabras clave:** *Síndrome coronario agudo. Unidades de dolor torácico. Inhibidores de la glucoproteína IIb/IIIa. Clopidogrel. Heparinas de bajo peso molecular. Estrategia invasiva.*

## INTRODUCTION

The Clinical Practice Guidelines must be an up-to-date reference document, and relevant clinical changes must be made periodically to the original document.

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Since the publication of the last edition of the Guide in 1999,<sup>1</sup> various studies have been published that report new data regarding management of the acute coronary syndrome (ACS) that are being incorporated into clinical practice and therefore must not be ignored. The Ischemic Cardiopathy and Coronary Unit Section has created a document on Chest Pain Units<sup>2</sup> that includes management of ACS in the emergency room that was not included in the original version of the Guide.

There is not a new edition of the Guide, but rather an Addendum to the Guide with regard to 3 concrete

**ABBREVIATIONS**

- ASA: acetylsalicylic acid.
- CRS: coronary revascularization surgery.
- AMI: acute myocardial infarction.
- CI: confidence interval.
- PCI: percutaneous coronary intervention.
- RR: relative risk.
- ACS: acute coronary syndrome.
- ACSWEST: acute coronary syndrome without ST elevation (encompasses the old term unstable angina/infarct without ST elevation).
- CPU: chest pain unit.

aspects: 1) the concept of a Pain Unit in the management and initial categorization of ACS in the emergency room; 2) an update on the indications for IIb/IIIa glycoprotein inhibitors (GP; clopidogrel and low molecular weight heparin in ACS), and 3) changes in the indication for coronary angiography and revascularization in this context.

The text of these 3 sections should be substituted for the text in the original Guide which otherwise remains in effect.

The complete text of the Guide is not included here, but only those part concerning the subjects being updated. To make it clearer for the reader, the heading always includes the subsection heading where the text has been changed. The beginning page number corresponding to the original version of the Guide<sup>1</sup> is indicated in brackets. If the heading for the subsection has been changed, the old heading will appear first in *italics* and will be followed by the new heading, in roman type. In the text of the modified subsection the original Guide text that is still in effect will appear in *italics* and the new text being added or substituted will appear in roman type.

The complete text of the revised Guide can be found on the Sociedad Española de Cardiología (SEC) web page (www.secardiologia.es).

**PRE-HOSPITAL PHASE AND EMERGENCY ROOM AREA**

***Conduct in the face of non-traumatic chest pain suggestive of angina or equivalent symptomatology in the hospital emergency room [page 840]***

**Chest pain units (CPU) (new text)**

Chest pain is the most common clinical manifestation of ACS, but it is also the most frequent cause of emergency room visits (5% to 20% of patients who go to the emergency room complain of chest pain).<sup>3</sup> It is necessary to quickly discriminate between patients presenting with ischemic myocardial pain and those who have pain stemming from other causes. In many patients with myocardial ischemia, the result of treatment is determined by how quickly the treatment is initiated.

The most accepted current method for improving the diagnosis and treatment of chest pain in the emergency room is the creation of CPUs.<sup>4</sup> The principal objective of these units is the rapid classification of patients into different risk groups. This classification should be completed within 30 minutes, and is later followed by an initial diagnostic evaluation in 6 to 9 hours. Patients with an unclear diagnosis should be kept under observation for 9 to 24 hours. The 3 phases of chest pain evaluation in the CPU are as follows:

**1<sup>st</sup> phase. Rapid classification of patients with acute chest pain**

In this first phase, direct clinical data and an electrocardiogram (ECG), performed within 10 minutes of admission, are used and the patients are placed in 1 of 4 categories with direct implications with regard to hospital admission (Table 1).

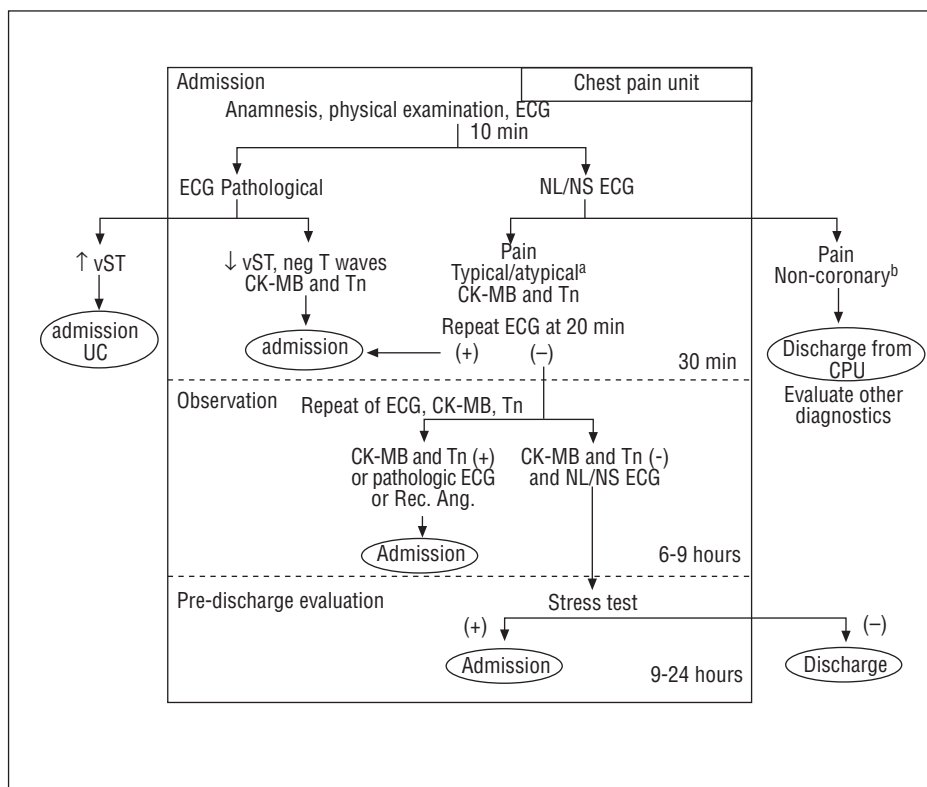
**2<sup>nd</sup> phase. Initial diagnostic evaluation**

Once the first phase has been completed, proceed to a better approximation of a diagnosis incorporating

**TABLE 1. Rapid classification of patients with acute chest pain upon arrival at the chest pain unit**

Risk group	Clinical ACS	Electrocardiogram	Destination/admission
1	Yes	ST elevation or LBB	Coronary unit
2	Yes	ST decline or negative T	Coronary unit/floor
3	Yes	Normal or non-diagnostic	Chest pain unit
4	No	Normal or non-diagnostic	Discharge/other areas

LBB indicates left branch block; ACS, acute cardiac.



**Fig. 1.** Protocol proposed by the Section of Ischemic Cardiopathy and Coronary Units of the SEC for the diagnosis of non-traumatic chest pain in the chest pain unit (modified by Bayón Fernández et al2). aConsider admission in the case of pain suggestive of myocardial ischemia with the presence of risk factors: myocardial infarct or prior coronary revascularization, cardiac insufficiency, or involvement of other vascular areas. bDiscard aortic dissection and pulmonary thromboembolism. NL/NS ECG indicates normal/non-diagnostic ECG; Tn, troponins; Rec Ang, recurrent angina.

biological markers, clinical signs, and the ECG.<sup>5</sup> This is based on data obtained from:

1. Anamnesis and physical examination. The existence of any of the following increases the likelihood myocardial ischemia: a) characteristic pain or the presence of vegetative signs; b) equivalent symptoms in diabetics, the elderly, or patients with prior cardiac insufficiency; c) accompanying symptoms such as left ventricular insufficiency, arrhythmias, or syncope, and d) factors such as age, cardiovascular risk factors, a history of ischemic cardiopathy, or the involvement of other vascular areas.

2. The ECG. This has greater diagnostic value if performed during an episode of pain. The patient in this unit receives serial ECGs and, if possible, is under continuous control. It must be underlined that: a) a normal or non-specific ECG indicates low risk, but does not exclude the diagnosis of myocardial ischemia;<sup>6,7</sup> b) a transitory or sustained elevation or decline in ST suggests a greater probability of myocardial ischemia and greater risk,<sup>8,9</sup> and c) T-waves have less significance.<sup>10</sup>

3. Indicators of cardiac damage. The appearance in peripheral blood of intracellular markers is diagnostic for myocardial damage. The 3 most useful markers are: a) myoglobin, which is the earliest marker. It is very sensitive and not very specific. A negative value during the first 4 to 8 hours precludes myocardial ne-

crois;<sup>11</sup> b) troponin (T or I) that begins to increase at 4 to 6 hours. This is very specific for myocardial damage, although it is not pathognomonic of ACS and has prognostic value.<sup>12</sup> If it is initially negative, it should be repeated at 8 to 12 hours from the start of symptoms, and c) the CK-MB mass, which, according to the National Academy of Clinical Biochemistry,<sup>13</sup> begins increasing at 4 to 5 hours and is less sensitive than troponin, but specific with regard to myocardial necrosis.

With this initial data the patients are classified into 3 diagnostic groups that form the basis for the initial ACS treatment algorithms (Figure 1):

1. Patients with ASC (with or without ST elevation). In this first group, patients with ST elevation must be treated immediately with coronary reperfusion.<sup>14</sup> Patients with ASC without ST elevation (ACSWEST) and risk markers must be admitted and treated according to the recommendations of this Guide.

2. Patients with non-coronary chest pain. These patients are managed according to their etiology.

3. Patients with chest pain of uncertain etiology. Once the patients with an admitting diagnosis of ACS and those with chest pain of another etiology have been identified, approximately one-third of patients will be left who do not have a clear diagnosis; for the majority of protocols, this is the population that should

be followed in the Chest Pain Unit. If the ECG continues to be normal, the patients should remain under observation and the ECG and tests for markers of necrosis should be repeated at 6 to 8 hours. On the other hand, if there are ischemic changes on ECG, the markers become positive, or there is a new episode of angina, the patient should be admitted. The recommended observation period varies from 6 to 24 hours.

### 3<sup>rd</sup> phase. Final evaluation in the CPU

Approximately 70% of patients admitted into the CPU and are observed for 6 to 24 hours have negative markers for necrosis, do not show changes on serial ECG, and do not show signs of hemodynamic instability.<sup>15</sup> Nevertheless, up to 3% of these patients could have an ACS and should not be discharged. For this reason, most protocols include an ischemia provocation test in the evaluation of patients in the CPU. Patients with a positive ischemia provocation test should be admitted and treated according to this Guide (Figure 1). Patients with a negative ischemia provocation test are in a low-risk group and can be treated in as outpatients.

## PRE-HOSPITALIZATION PHASE AND THE HOSPITAL EMERGENCY ROOM

### *Proposed classification for risk categorization [page 841]*

#### **Risk categorization in patients admitted with confirmed ACS (new text)**

The risk in for this group of patients with ACS refers to the probability of death, development of an acute myocardial infarction (AMI), refractory ischemia, or ventricular arrhythmias during the subsequent 30 days.

The evaluation of the probability of an immediately unfavorable course is based on the existence of risk criteria. Patients are divided into 3 groups with different prognoses and therapeutic management protocols:

1. High-risk groups: patients who present with any of the following criteria:

- Hemodynamic instability: shock, acute pulmonary edema, arterial hypotension, or mitral insufficiency.
- Recurrent angina with adequate treatment.
- Resting angina with ST segment changes  $\geq 1$  mV during the crisis.
  - Marked or persistent ST segment changes.
  - Markedly elevated troponin (troponin T=10 times the median normal value [ $0.01 \times 10 = 0.1$  ng/ml]). For

troponin I there are several methods with different values that can be used, but the 10 times normal value level is also valid as a criterion).<sup>16,17</sup>

- Post-infarct angina.
- Serious ventricular arrhythmias.
- FEVI < 0.35.

2. Intermediate risk group: patients who do not have any of the previous criteria, but do have 1 of the following:

- Angina at rest or prolonged angina with ECG changes in the previous 24 to 48 hours.
- Angina at rest with decline of the ST segment < 1 mV.
- Deep negative T-wave of various derivations.
- History of myocardial infarction or coronary revascularization.
- Involvement of other areas (cerebral, periphe-  
ral...).
- Diabetes mellitus.
- Age > 70 years.
- Moderately elevated troponin (TnT  $\geq 0.01$ ; < 0.1).<sup>16,17</sup>

3. Low risk group: patients with none of the preceding criteria or circumstances. This category allows application of a therapeutic management algorithm proposed in this Guide update (Figure 2).

## MANAGEMENT OF THE PATIENT WITH UNSTABLE ANGINA/AMI WITHOUT ST SEGMENT ELEVATION IN THE CORONARY CARE UNIT

### Pharmacologic treatment

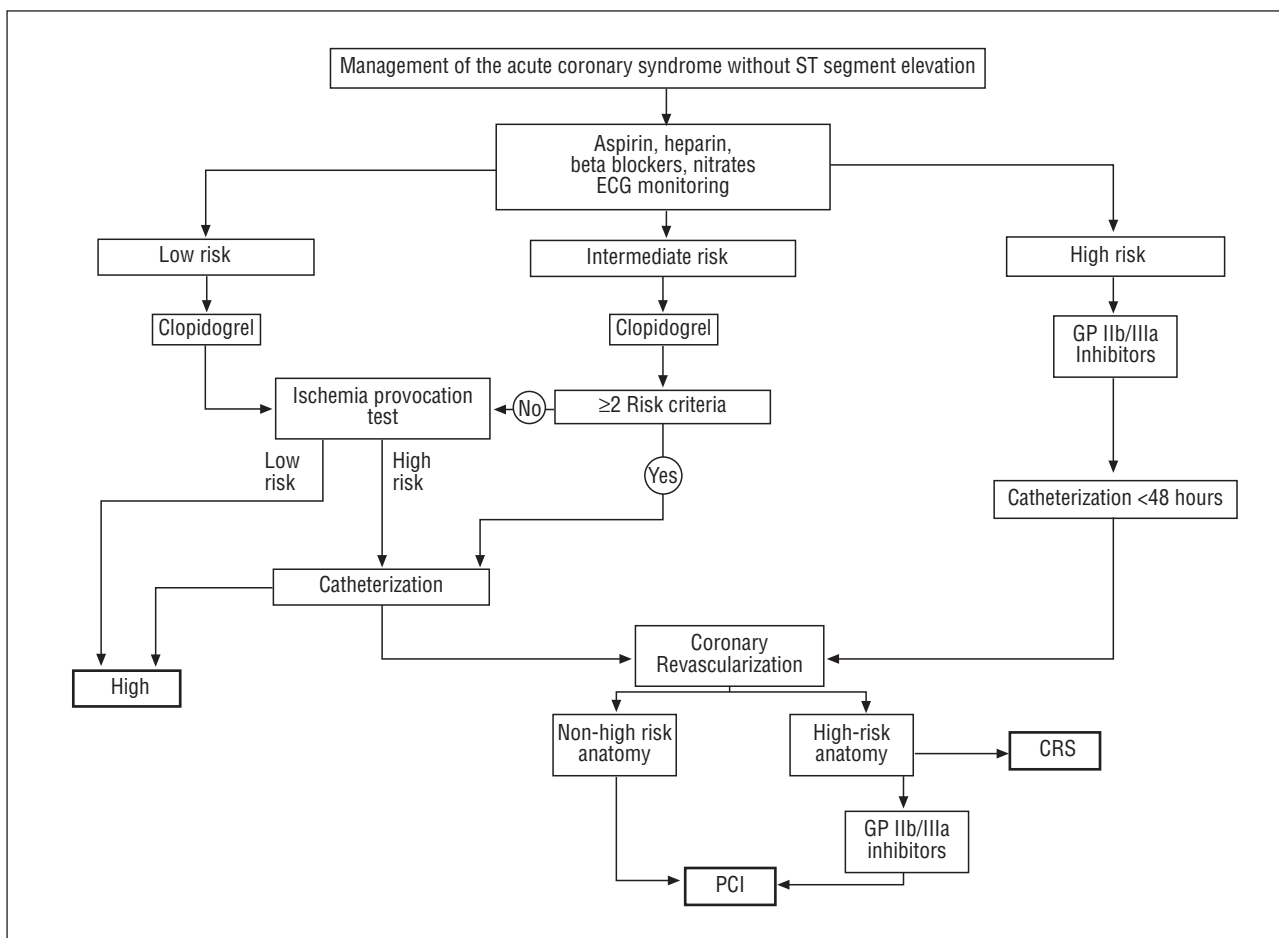
#### *Anti-aggregate plaque treatment [page 842]*

(see original Guide text for aspirin, ticlopidine, and triflusal)

(New text added):

#### **Clopidogrel**

Clopidogrel is a new tienopyridine derivative that has less side-effects than ticlopidine. It has not yet been directly proven effective as a substitute for acetylsalicylic acid (ASA) for the initial treatment of ACSWEST, but its efficacy has been inferred by trials in other clinical situations. It has directly demonstrated its efficacy as a substitute for acetylsalicylic acid in long-term secondary prevention. It is also considered as having efficacy similar to ticlopidine with better tolerance. American guidelines extrapolate the results of the CAPRIE<sup>18</sup> study for pa-



**Fig. 2.** Proposed scheme for the management of ACSWEST. The algorithm is based on the categorization of patients into risk groups (see text). CRS indicates coronary revascularization surgery; GP, glycoprotein; PCI, percutaneous coronary intervention.

tients with ACS and aspirin intolerance a Class I recommendation.

The CURIE study<sup>19,20</sup> compared the clinical course of 12 562 patients with ACSWEST randomly assigned within the first 24 hours to groups of treatment with aspirin (75 to 325 mg/day) or ASA associated with clopidogrel (300 mg loading dose the first day and then 75 mg/day) with a mean followup period of 9 months. The patients assigned to treatment with aspirin and clopidogrel showed an absolute reduction in the incidence of death, infarct, or cerebrovascular accident of 2.1% (relative risk [RR]=0.80, 95% confidence interval [CI], 0.72 to 0.90). The rate of major hemorrhages was greater in those patients with combined treatment (1% in absolute terms), although the rate of life-threatening hemorrhages did not increase in this group. Although the risk groups were not defined in the study and the authors themselves advised that the analysis of the subgroups should be undertaken with caution, it appears that the groups who received the most benefit were the medium-risk and low-

risk groups and those patients with a history of coronary vascularization. Therefore, the administration of clopidogrel would be indicated in intermediate-risk and low-risk (class I) patients with ACSWEST. In high-risk patients with ACSWEST, the risk to benefit ratio should be evaluated when they receive GP IIb/IIIa inhibitors, as the effects of taking clopidogrel in association with these drugs is unknown at present.

The data from the patients in the CURE study who underwent percutaneous revascularization were specifically analyzed in a parallel publication.<sup>20</sup> The incidence of refractory ischemia or infarct was reduced by 24% (3.2% in absolute terms;  $P=.008$ ) and for infarct by 32% (1.5% in absolute terms) in the period between diagnosis and intervention. The mortality or infarct rate up to 30 days following angioplasty was 30% less in those patients who were treated with clopidogrel. The administration of clopidogrel later was not associated with a significant benefit. Therefore, clopidogrel is indicated before intervention if the patient has not received treatment with GP IIb/IIIa inhi-



bitors and for all patients during the 30 days following angioplasty, especially if a stent (class I) is used.<sup>21</sup> Clopidogrel has been proven to be as effective as ticlopidine in the prevention of thrombotic stent occlusion after implantation.<sup>22</sup> After more than 30 days following angioplasty, clopidogrel administration is not justified according to current data (class IIb). Heart surgery in these patients is associated with a major perioperative hemorrhage, and the effect of this on an increase in complications is pending study. Nevertheless, the suspension of treatment for several days prior to revascularization surgery appears advisable.

Administration of intravenous glycoprotein IIb/IIIa inhibitors [page 843] (*original text appears in italics and text that has been added in normal type*):

For the management of ACS without ST elevation, 4 intravenous glycoprotein GP IIb/IIIa plaque inhibitors have been tried: eptifibatide, tirofiban, lamifiban, and abciximab, all of which are used as complementary therapy added to ASA and, in the majority of cases, also in addition to heparin.

1. Eptifibatide. *The PURSUIT<sup>23</sup> study included 10 948 patients with ACS and was the study with the greatest number of patients with this pathology that randomized patients to treatment with eptifibatide or placebo in addition to standard treatment. The study showed a significant reduction (1.5% in absolute terms) in the incidence of death or nonfatal infarct evident at 92 hours, and the rate remained at a similarly significant rate at 30-day and 6-month followup. The broad inclusion criteria for this study allowed representation of all risk levels found habitually in clinical practice, and allowed the results to be extrapolated to patients seen in daily practice. Nevertheless, the analysis of subgroups revealed that efficacy was greater in high-risk patients, and especially in those in whom coronary intervention was performed within the first 24 hours.<sup>24</sup> Therefore, the administration of eptifibatide is recommended as class I in high-risk patients with ACSWEST in whom the intention is to perform coronary revascularization within the next 48 hours, and as class IIa in those high-risk patients who will not undergo early revascularization. The indication for patients who are not high-risk is class IIb. A retrospective analysis of the PURSUIT study shows an important increase in the risk of major hemorrhages without any benefit (non significant increase in death and AMI) in patients older than 80 years of age (class III).<sup>25</sup>*

2. Tirofiban. *The PRISM-PLUS study<sup>26</sup> included 1915 high-risk patients with unstable angina randomized to treatment with tirofiban, heparin, or tirofiban plus heparin. Intravenous tirofiban showed an absolute*

*decrease in the incidence of ischemic events, defined as death, AMI, and recurrent ischemia, at 7 days (5.3%), 30 days (3.5%), and 6 months (2.2%) when this inhibitor was accompanied by heparin and ASA. The benefit was most notable in high-risk patients, particularly those who underwent early revascularization (class I), and was not as obvious in those patients who did not undergo early revascularization (class IIa). The PRISM study, which included low-risk patients,<sup>27</sup> did not reveal a similar benefit when comparing the effect of tirofiban vs heparin. The benefit of tirofiban in patients with ACSWEST who are not high-risk is doubtful (class IIb), although information is not available on the elderly.*

3. Lamifiban. *In the PARAGON study,<sup>28</sup> a research study on the intravenous lamifiban dose, no significant differences were found in favor of active treatment at 30 days. These results were repeated in the PARAGON study<sup>29</sup> of 5225 patients (absolute reduction was 1%, not statistically significant, with an increase in hemorrhages), so that its use is not indicated (class III).*

4. Abciximab. *The GUSTO IV ACS study<sup>30</sup> randomized 7800 patients with ACSWEST to receive placebo or an abciximab infusion for 24 or 48 hours. It was recommended that performing coronary angiography during the infusion be avoided. No benefit of treatment with abciximab was observed, and there was a greater absolute incidence of the study outcome (death and AMI at 30 days) in those who received the prolonged abciximab treatment (1.1%;  $P=.19$ ). Therefore administration of abciximab in patients with ACS outside the hemodynamic laboratory setting is contraindicated (class III).*

GP IIb/IIIa inhibitor recommended according to the moment of performing percutaneous coronary intervention (PCI). GP IIb/IIIa inhibitor drugs are effective for the reduction of ischemic complications in patients with ACSWEST. Nevertheless, these drugs have shown the greatest benefit in patients who undergo a PCI. In this situation, nevertheless, not all inhibitors have shown the same level of efficacy.

Among the various inhibitors, abciximab is the antagonist that has demonstrated the most consistent marked benefit in different situations associated with PCI, both with conventional balloon angioplasty (EPIC, CAPTURE, and EPILOG studies)<sup>31-33</sup> and in procedures involving stent implantation (EPISTENT study)<sup>34</sup> Tirofiban and eptifibatide (RESTORE and IMPACT studies, respectively)<sup>35,36</sup> demonstrated a modest level of efficacy in studies of conventional angioplasty. Nevertheless, recently study outcomes have shown that eptifibatide is associated with a marked reduction in ischemic complications during the performance of pro-

cedures involving stent implantation in moderate and low-risk patients (ESPRIT study).<sup>37</sup> The only comparative study of 2 GP IIb/IIIa inhibitors in PCI with stent implantation has shown a greater benefit with abciximab than with tirofiban.<sup>38</sup>

A finding that supports these studies is the fact that these drugs are most effective principally during the first 24 to 48 hours following the procedure, and they predominantly reduce the incidence AMI of modest or moderate involvement. In the same manner, the studies cited have revealed that subgroups of patients, who can be identified clinically or by predetermined angiographic characteristics, may benefit much more significantly from GP IIb/IIIa inhibitors.

Keeping in mind the existing relationship between the GP IIb/IIIa inhibitors and the moment at which the PCI is performed in patients with ACSWEST, the recommendation of the inhibitor may be related to the timing of the interventionist procedure, when this is indicated:

– If the PCI can be done within the first 4 to 6 hours, the initiation of administration of the GP IIb/IIIa inhibitor can be postponed until the results of the coronary angiography are known. If the PCI is feasible and the patient meets the clinical or anatomical criteria indicating the use of a GP IIb/IIIa inhibitor, abciximab administered before the procedure and maintained in perfusion up to 12 hours following the procedure (class I) shows a clear reduction in the incidence of ischemic complications. Eptifibatide can also offer a significant benefit in this situation (class IIa). If PCI is not feasible and the clinical and anatomical risks are high, eptifibatide or tirofiban may be indicated.

– If the PCI cannot be performed within the first few hours, it is recommended that eptifibatide or tirofiban be started and coronary angiography be performed as soon as possible. If PCI is feasible, the administration of the same GP IIb/IIIa inhibitor should be continued during and after the procedure, with perfusion being maintained for 18 to 24 hours. If PCI is not feasible and the clinical and anatomical risks are high, it is recommended that the GP IIb/IIIa inhibitor initially administered be continued. In the reverse situation it should be suspended.

Patients with ACSWEST on whom PCI is performed who are not previously being treated with GP IIb/IIIa inhibitors. The routine administration of GP IIb/IIIa inhibitors in all PCI procedures in patients with ACSWEST shows a statistically significant, although clinically modest, benefit. Therefore, attempts have been made to identify the patient subgroups who would most benefit from the administration of GP IIb/IIIa inhibitors and those in whom their indication would be most worthwhile. Patients who undergo PCI with high-risk clinical (refractory angina, increased

markers for myocardial damage, etc.) and anatomical (complex lesions, diffuse coronary disease) criteria obtain a considerable reduction in the incidence of ischemic episodes with the administration of GP IIb/IIIa inhibitors at the moment the interventionist procedure is begun (class I). In this situation, abciximab has consistently shown a marked benefit. The usefulness of the non-elective administration of GP IIb/IIIa inhibitors during or at the end of the PCI procedure has not been demonstrated in controlled studies; nevertheless, there are situations involving a high risk of ischemic complications in which their administration would probably be beneficial.

### Anticoagulant treatment

*Low molecular weight heparin [page 843] (original text in italics and text that has been added in normal type).*

1. Enoxaparin (class I in acute phase). *The ESSENCE study<sup>39</sup> randomized 3171 patients to receive enoxaparin or non-fractionated intravenous heparin during the hospital phase for a period from 48 hours to a maximum of 8 days. After 14 and 30 days the outcomes, consisting of death, non-fatal AMI, recurrent angina, or the need for revascularization, were significantly lower in the group that received enoxaparin (16.5% vs 19.8% in the heparin group at 14 days; 19.8% vs 23.3% in the heparin group at 30 days) without increasing the risk of severe hemorrhage. The recommended dose is 1 mg/kg/12 hours subcutaneously.*

In the TIMI-11B study<sup>40</sup> 3910 patients were randomized to receive non-fractionated heparin or enoxaparin in the acute phase and the outpatient phase. The primary outcome (death, AMI, or urgent revascularization) was evaluated at 8 and 43 days. At 8 days, a statistically significant reduction in the outcome was observed in the patients treated with enoxaparin vs those treated with heparin (12.4% vs 14.5%;  $P=.048$ ); this difference that was maintained at 43 days (17.3% vs 19.7%;  $P=.048$ ), indicating that there was no added benefit to prolonged treatment, although the occurrence of major hemorrhages was increased. Therefore, prolonged treatment with this drug is not indicated (class III). In patients with renal insufficiency, the available data is scarce but supports a 64% reduction in the enoxaparin dose when creatinine clearance is less than 30 ml/min.<sup>41</sup>

2. Dalteparin (class I in the acute phase). *In the acute phase, 3 randomized control studies with placebo have evaluated the benefit of low molecular weight heparin for the treatment of unstable angina and non-Q-wave AMI. The FRISC study<sup>42</sup> compares the use of dalteparin in association with ASA vs ASA alone. The patients randomized to dalteparin received 120 UI/kg in 2 subcutaneous doses per day for 6 days during the*

acute phase, and a fixed subcutaneous dose 2 times a day for 35 to 45 days during the chronic phase. Dalteparin decreased the incidence of death and myocardial infarction on the sixth day (from 4.8% in the placebo group to 1.8% with dalteparin). Nevertheless, this difference was no longer significant at 40 days and was not present at all at 6 months. The FRIC study<sup>43</sup> included in the first, open, phase, 1482 patients who were randomized to receive dalteparin at an identical dose as in the previous study, or non-fractionated heparin, for at least 48 hours. The second phase was randomized (dalteparin, fixed dose of 7500 UI subcutaneously, twice a day or placebo), double blind, and lasted 45 days. No significant differences were found in any phase of the study in the decrease of ischemic events among the heparin, dalteparin, or placebo groups.

Finally, the FRISC II study<sup>44</sup> evaluated the efficacy of long-term treatment (3 months) with dalteparin vs placebo in 2267 patients. Dalteparin was administered to all patients in the acute phase for a minimum of 5 days. Although a reduction in death or AMI was observed at 30 days in the group that received dalteparin (3.1% vs 5.9%;  $P=0.002$ ), at 3 months there was no reduction (6.7% in the dalteparin group vs 8.0% in the placebo group,  $P=0.17$ ). In the total patient cohort a reduction was observed at 3 months in the incidence of death, AMI, and the need for revascularization in the dalteparin group (29.1% vs 33.4%;  $P=0.031$ ), but this association of events had not been defined as a study objective. These benefits were not maintained at 6 months. Therefore, dalteparin would probably be indicated in patients awaiting invasive procedures (class IIa).

3. *Nadroparin* (acute phase class I). In 1995 Gurfinkel et al<sup>45</sup> demonstrated that nadroparin added to ASA significantly decreased the incidence of death, recurrent angina, or the need for revascularization vs ASA alone (22% vs 59%) during the acute phase of unstable angina or non-Q-wave AMI. The FRAXIS study<sup>46</sup> investigated the effect of prolonged treatment with nadroparin in a total of 3468 patients treated with aspirin and randomized to treatment with non-fractionated heparin for 6 days, nadroparin for 6±2 days, and nadroparin for 14 days. There were no significant differences between the 3 groups in the incidence of cardiac events (cardiac death, AMI, refractory angina, or recurrence of unstable angina at 14 days). There was an increase in the risk of a major hemorrhage in the group that received nadroparin for 14 days, as compared to the group that received non-fractionated heparin. The indication of the chronic phase is class III.

Combination of low molecular weight heparin and GP IIb/III inhibitors. The use of antiaggregant and anti-thrombotic drugs constitutes the cornerstone of

treatment of ACSWEST. Several studies have demonstrated the efficacy of these drugs. The association between them, interesting from a physiopathological point of view, must guarantee an increase in efficiency without reducing safety. Cohen et al<sup>47</sup> compared the combination of ASA, tirofiban, and enoxaparin with the combination of ASA, tirofiban and non-fractionated heparin in 55 patients with ACSWEST. The level of inhibition of plaque aggregation was more uniform and the hemorrhage occurrence was slightly lower in those patients treated with enoxaparin (1 mg/kg/12 hours) than in those treated with non-fractionated heparin. The ACUTE II study, pending publication, established the safety of the combination of tirofiban and enoxaparin (315 patients) compared to non-fractionated heparin (210 patients). There are randomized studies in progress with a sufficient number of patients to evaluate the combination of low molecular weight heparin and GP IIb/IIIa inhibitors (TETAMI,<sup>48</sup> A to Z<sup>49</sup>), but the results are not yet available.

Low molecular weight heparin in patients with ACSWEST. Recently published clinical data indicate that enoxaparin provides effective anticoagulation in patients with ACSWEST subjected to PCI, without an increase in major hemorrhagic complications.<sup>50</sup> In the NICE 1 and NICE 4 studies,<sup>51</sup> the association of abciximab (0.25 mg/kg in bolus, followed by a perfusion of 0.125 µg/kg/min for 12 hours) and an intravenous bolus of enoxaparin (1 mg/kg in NICE 1 and 0.75 mg/kg in NICE 4) were analyzed during PCI. More than 1600 patients were included, and the results indicate that this therapeutic combination appears to be safe and effective. The results of the NICE 3 study<sup>52</sup> have been communicated (but not published) and appear to extend the good results obtained with the combination of enoxaparin to the use of eptifibatid and tirofiban.

#### **MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA/AMI WITHOUT ST SEGMENT ELEVATION IN THE CORONARY CARE UNIT [PAGE. 842] AND ON THE HOSPITAL CARDIOLOGY FLOOR [PAGE. 845]**

***Indications for coronary angiography and revascularization in the coronary care unit [page 845] and indications for coronary angiography on the floor [page 848] (new text):***

#### **Invasive strategies vs conservative strategies**

At the beginning of the 1990s, 2 randomized studies (TIMI IIIB<sup>53</sup> and VANQWISH<sup>54</sup>) attempted to answer the question of whether in patients with ACSWEST



routine invasive treatment (systematic coronary angiography with revascularization, if possible) was better than conservative treatment (coronary angiography and revascularization only in those patients with recurrent spontaneous ischemia or ischemia induced by non-invasive tests). The results of these studies did not show superiority of the invasive strategy, but they were done before the introduction of 2 of the principal advances in PCI, intracoronary stents and GP IIb/IIIa inhibitors.

### Current indications for coronary angiography and revascularization

Two randomized studies published later caused a significant change in the treatment of patients with ACSWEST. The FRISC II study<sup>55</sup> was a randomized study that analyzed the influence on prognosis of a routine invasive strategy as compared to a conservative strategy in patients with ACSWEST. Two thousand four hundred and fifty-seven patients being treated with ASA and, initially, with dalteparin were included in the study. Coronary angiography was performed within the first 7 days (mean 4<sup>th</sup> day) in 90% of the patients in the invasive group and 10% of the patients in the conservative group. Revascularization was performed within the first 10 days in 71% and 9% of patients, respectively. Among the patients subjected to PCI, 61% and 70%, respectively, received intracoronary stents and 10% received treatment with abciximab. The incidence of ischemic events (death or infarct) at 6 months was significantly lower in the patients initially assigned to the invasive strategy group as compared to the conservative strategy group (9.4% vs 12.1%; RR=0.78; 95% CI, 0.62 to 0.98;  $P=.031$ ), an advantage that was maintained at 1-year followup (10.4% vs 14.%;  $P=.05$ ), suggesting a persistent beneficial effect of routine invasive treatment.<sup>56</sup>

The TACTICS-TIMI 18 study<sup>57</sup> randomized 2220 patients with ACSWEST to an initial invasive strategy (routine catheterization within the first 4 to 48 hours and revascularization if technically feasible) or a more conservative strategy (catheterization if recurrent ischemia was present or if a stress test was abnormal). All study patients were being treated with ASA, heparin, and tirofiban, systematically administered before randomization. At 6-month followup, the incidence of the primary outcome (death, non-fatal infarct, or readmission due to ACS) was significantly less in the patients initially assigned to the invasive strategy group than those randomized to the conservative strategy group (15.9% vs 19.4%; odds ratio (OR)=0.78; 95% CI, 0.62 to 0.97;  $P=.025$ ). The incidence of death or non-fatal infarct was also significantly lower (7.3% vs 9.5%;  $P<.05$ ). The study concluded that in patients with ACSWEST treated with tirofiban, an initial inva-

sive strategy significantly reduced the incidence of major ischemic events as compared with using a conservative strategy.

Both studies also identified certain subgroups of patients in whom the benefit of a routine invasive strategy has an important effect on the prognosis. Patients with changes on initial ECG and patients with an increase of myocardial damage markers (troponins)<sup>15</sup> were the subgroups in both studies that showed a marked benefit with the initial use of an invasive strategy.<sup>55,57</sup>

Keeping in mind the studies mentioned, the recommendation as to what strategy to follow can be adapted to different types of hospitals without causing a significant change in the benefit of the initial invasive strategy.

1. Strategy in hospitals with the availability of coronary angiography and PCI *in situ*. In these centers, an interventionist strategy can be applied (coronary angiography and revascularization, of technically feasible) for patients clinically classified as high-risk (class I). Among these, the patients with changes on initial ECG or increase in markers of myocardial damage would significantly benefit from an initial invasive strategy.<sup>55,57</sup> It is recommended that these procedures be performed within the first 24 to 48 hours after diagnosis. In those patients with intermediate risk criteria, an invasive strategy is preferable, although the time interval between diagnosis and procedure can be longer (within the first 4 days). In the same manner, coronary angiography and if possible revascularization are recommended for those patients without other risk factors in whom non-invasive tests are positive for ischemia or if other criteria indicative of a poor prognosis are present. The following patients should be excluded from this strategy: patients in whom the episode of instability could have been triggered by a non-cardiac cause (renal insufficiency, hyperthyroidism, anemia, etc.) and patients with known coronary anatomy that would not be susceptible to coronary revascularization.

2. Strategies in hospitals where coronary angiography and PCI *in situ* is not possible. Patients with ACSWEST categorized as high risk admitted to these centers must be transferred to hospitals where coronary angiography and PCI can be performed as soon as possible (class I).<sup>55,57</sup> Transfer must be made within 48 hours of making the diagnosis. For patients with various intermediate risk criteria, the transfer can be delayed up to 4 days. An adequate clinical evaluation with non-invasive tests must allow identification of the patients who must be transferred for performance of coronary angiography or revascularization before discharge. As for the previous group, coronary angiography and possible revascularization is recommended in patients whose non-invasive tests are positive for is-

chemic or other criteria resulting in a poor prognosis, although other risk factors may not be detected. The interval for performance of coronary angiography or PCI in these patients can be longer.

## FINAL COMMENTARY REGARDING THE RECOMMENDATIONS AND THEIR ASSOCIATED IMPLICATIONS

### Pharmacological recommendations co-occur with class I recommendations

Class I recommendations must always be considered the first choice when they are clinically applicable. In this and other guides there are certain clinical situations in which there are various drug recommendations that co-occur with class I recommendations. The majority are made for each drug individually and concurrent administration of several or all drugs is not recommended. In the majority of cases, there is no evidence of a beneficial effect from their simultaneous administration or even their compatibility, as at the moment there have not been enough studies published in this regard. For this reason, it is necessary to have a clinical sense of the individual patient in order to prescribe adequate treatment. In this Guide, this situation exists for the indication of antiaggregant plaque and anti-thrombotic drugs in the acute phase of ACS-WEST: non-fractionated heparin, low molecular weight heparin, aspirin, tienopyridine, and GP IIb/IIIa inhibitors. There are studies currently underway that will provide new evidence to update and possibly modify these recommendations.

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