Editorial

Comments on the ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting With Persistent ST-Segment Elevation

Comentarios a la guía de práctica clínica de la ESC para el manejo del infarto agudo de miocardio en pacientes con elevación del segmento ST

Spanish Society of Cardiology Working Group on the Clinical Practice Guidelines for ST-Elevation Acute Coronary Syndrome

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INTRODUCTION

The European Society of Cardiology (ESC) guidelines are endorsed by the Spanish Society of Cardiology (SEC) and translated into Spanish for their publication in the Revista Española de Cardiología. Under the policy introduced in 2011, each new guideline is accompanied by an article that formulates comments in accordance with the objectives and methodology recommended in the article that established the Guidelines Committee of the SEC.

In the present article, we discuss the new European guidelines for ST-segment elevation acute myocardial infarction (STEMI). The Guidelines Committee established a work group composed of members proposed by the Ischemic Heart Disease, Hemodynamics, Clinical Cardiology, Heart Failure, and Geriatric Cardiology work groups.

As a general comment, we consider that the present guidelines introduce highly interesting developments and that the topics are dealt with clearly and in detail. However, we should also point out that it contains 157 recommendations, 69 (44%) of which are accompanied by level C evidence (expert consensus), predominantly in the sections on in-hospital management, heart failure, and complications, fields in which there thus remains ample room for individualization and progress in clinical research. In applying them, we should not forget that the guidelines themselves remind us that the level A and B recommendations are based on clinical trials, and that even these results are open to interpretation. The different therapeutic options could be influenced by the available resources. Thus, it will be increasingly necessary to perform cost-efficiency studies that aid us in choosing among the different strategies.

For the purpose of making the article more readable and to highlight the most relevant or novel aspects, as well as those that are not made clear or are not addressed, we have summarized them in Tables 1 and 2, respectively.

INITIAL MEASURES

The guidelines especially stress the prevention of delays in treatment. When STEMI is suspected, it is essential to facilitate rapid access to defibrillation during the initial moments, if indicated, and guarantee earlier access to reperfusion. The new position is that the first therapeutic option for patients resuscitated from sudden cardiac death and who have ST-segment elevation is the performance of primary angioplasty, provided the recommended time intervals are met. Moreover, the guidelines point to evidence showing that patients who remain in coma after resuscitation from out-of-hospital cardiac arrest benefit from therapeutic hypothermia, provided it is initiated early.

This section refers to cases of suspected coronary occlusion without ST-segment elevation which, on occasion, can be extremely serious (occlusion of left main coronary artery, of a saphenous vein bypass graft to circumflex artery, etc.), but can sometimes correspond to noncoronary disease. This aspect has been addressed previously in the guidelines for non-ST-elevation acute coronary syndrome, which...
stress the importance of the cardiologist in documenting the clinical history as well as the need for an emergency echocardiogram.

We consider the recommendation that all hospitals that provide care to STEMI patients record time-to-treatment and regularly review the data to ensure that they are complying with the recommendations. In addition, the publication of these data (times of symptom onset, first medical contact, performance of electrocardiogram, initiation of reperfusion, etc.) may be useful in stimulating improvements in health care. The practice of showing the results of health care processes is not widespread either in Spain or in Europe as a whole.

The guidelines introduce the novel idea that the out-of-hospital emergency medical service plays an essential role in the entire health care process and that it must be considered not only a mode of transport, but a space for the initial diagnosis, triage, and treatment. Thus, ambulance services should be capable of performing electrocardiograms, treating pain, maintaining hemodynamic stability, carrying out resuscitation maneuvers if necessary, triaging the patient to the most appropriate center, and initiating reperfusion therapy in the case of fibrinolysis, as well as adjunctive antiplatelet therapy in the case of primary angioplasty. In Spain, some communities have had highly efficient management protocols for years. We should keep in mind that these protocols, while adapted to the special characteristics of each region, should remain faithful to the basic recommendations of the ESC, especially with respect to the target times.

Thus, the optimal treatment of STEMI is based on an efficient out-of-hospital emergency service and a good network of interconnected hospitals of different levels. The keys to the effectiveness of this organization are:

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**Table 1**

2012 European Society of Cardiology Guidelines for the Treatment of ST-Segment Elevation Acute Myocardial Infarction. Most Relevant and/or Novel Aspects

| Initial measures | • Primary angioplasty is indicated after resuscitated sudden cardiac death and ST-segment elevation (IB)
| Reperfusion therapy | • Reperfusion therapy is indicated for all patients whose symptoms started <12 hours earlier (IA)
| Management during hospitalization and at discharge | • Introduction of the phrase “strict, but not too strict” management of hyperglycemia during the acute phase, avoiding episodes of hypoglycemia
| Complications | • Inclusion of sodium nitroprusside for patients with HF and HT (IIa C) and of hydralazine and nitrates for those who do not tolerate ACE inhibitors and ARB (IIa C)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; FMC, first medical contact; GPIIb/IIIa, glycoprotein IIb/IIIa; HF, heart failure; HT, hypertension; PCI, percutaneous coronary intervention.

(a)The items for which the class of recommendation and level of evidence are not specified appear in the original text of the guidelines without that information.

(b)Massive angiographic thrombus, failure to reestablish myocardial perfusion (no-reflow phenomenon), or thrombotic complication.

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**Table 2**

2012 European Society of Cardiology Guidelines for the Treatment of ST-Segment Elevation Acute Myocardial Infarction. Aspects Not Clarified and Aspects Not Addressed

| Initial measures | • Primary angioplasty-hypothermia sequence in out-of-hospital cardiac arrest
| Reperfusion therapy | • In relation to primary angioplasty:
| Management during hospitalization and at discharge | • Decisions concerning return to occupational activity, sexual activity, air travel, etc.
| Complications | • Possibility that techniques for percutaneous VSD repair become an alternative or a bridging therapy to surgical treatment in selected cases

VSD, ventricular septal defect.
of stent, the guidelines stress the importance of selecting the proper size and recommend the use of drug-eluting rather than bare-metal stents (IIa A) if the patient has no contraindications for dual antiplatelet therapy and is likely to be compliant. However, they do not mention the eventual benefits of second-generation drug-eluting stents over first-generation or bare-metal stents. The presentation of these guidelines has been followed by the publication of 2 randomized studies (EXAMINATION* and COMFORTABLE-AMI*) that demonstrate the efficacy and safety of second-generation stents in this situation. Another new recommendation is the systematic use of aspiration catheters during the procedure. This indication has been changed from class IIb to IIa B. The results of remote conditioning and postconditioning studies are inconclusive. The different maneuvers undertaken to treat the failure to reestablish myocardial flow (no-reflow phenomenon) in the catheterization laboratory have also not been found to be sufficiently effective.

As a practical summary, it can be proposed that primary angioplasty be carried out using the radial approach, with thrombectomy, followed by implantation of a drug-eluting stent.

From the pharmacological point of view, one of the most novel aspects is the introduction of prasugrel and ticagrelor as antiplatelet drugs of choice (class IB for both), over clopidogrel (IC) which, in these guidelines, is relegated to situations in which prasugrel and ticagrelor cannot be administered or are contraindicated and to patients treated with fibrinolysis alone. The possibility of changing drugs in patients who have undergone clopidogrel loading prior to primary angioplasty is not mentioned in these guidelines. An important aspect, should coronary artery surgery be necessary in patients receiving these treatments, is the recommendation that surgery be postponed until 7 days after the discontinuation of prasugrel, 5 days in the case of clopidogrel, and 3 days to 5 days in the case of ticagrelor. In this situation, for those patients in whom the discontinuation of antiplatelet therapy is not advisable, the possibility of bridging therapy (with short half-life glycoprotein IIb/IIIa [GPIIb/IIIa] inhibitors) can be considered, although there is no clinical evidence to support its efficacy.

The use of GPIIb/IIa inhibitors in STEMI has been restricted to bailout therapy in the presence of massive intracoronary thrombus, in situations of no reflow, or in thrombotic complications (IIa C). Their systematic use on arrival in the catheterization laboratory is not recommended (IIa C). As another novel feature, the guidelines present the results of the INFUSE-AMI and AIDA trials, which compare intracoronary with intravenous administration of abciximab, revealing no clear differences between the 2 strategies.

The new development with respect to antiocoagulation therapy is the recommendation of bivalirudin as the agent of choice over heparin associated with GPIIb/IIa inhibitors, based on the reduced mortality observed at 30 days and for up to 3 years in the HORIZONS-AMI trial. The guidelines mention the interaction that the administration of unfractionated heparin prior to randomization may have had in the reduced risk of stent thrombosis in a considerable number of patients. The efficacy of bivalirudin administered in combination with prasugrel or ticagrelor is not known, since clopidogrel was the adenosine diphosphate (ADP) receptor antagonist used in that trial. In the ATOLL trial, enoxaparin, when compared with unfractionated heparin, reduced the incidence of the composite endpoint (30-day mortality, myocardial infarction, procedural failure, and bleeding), a fact that supports its recommendation as adjunctive therapy when bivalirudin is not employed. As a practical summary concerning adjunctive therapy in primary angioplasty, pretreatment of the patient with acetylsalicylic acid and prasugrel or ticagrelor is recommended (if there are no contraindications). Likewise, the favorable safety and efficacy profile of bivalirudin with respect to combined heparins and GPIIb/IIa inhibitors indicates that bivalirudin could be the anticoagulant of choice. Glycoprotein IIb/IIa inhibitors would be used in situations of higher thrombogenic risk.
4. Fibrinolysis: Adjunctive Antithrombotic Therapy and Invasive Treatments. Should angioplasty not be available within the target time, the benefit of prehospital fibrinolysis is increasingly evident, especially in patients who can be treated within 60 minutes of symptoms onset. The most relevant new feature, mentioned above, is the indication that once treated the patient be transferred immediately to a PCI-capable center, with the organizational implications that this entails. As adjunctive antiplatelet therapy, a combination of acetylsalicylic acid and clopidogrel is recommended, with enoxaparin as the anticoagulant of choice. Neither bivalirudin nor the new P2Y12 receptor antagonists have been studied in this context.

5. Treatment for Nonreperfused Patients. This section deals with patients who arrive at the hospital more than 12 hours after symptoms onset without persistent symptoms or ischemia, or those who cannot be reperfused for some clinical reason. The recommended antiplatelet therapy includes acetylsalicylic acid and clopidogrel, although ticagrelor is now added on the basis of the data of those patients in the PLATO trial who had not been revascularized. With respect to anticoagulant therapy, fondaparinux, enoxaparin, or unfractionated heparin is recommended at the same doses as those administered after fibrinolysis.

6. Special Clinical Situations. In patients with multivessel disease, in the context of the acute phase of STEMI, the recommendation is to treat only the culprit artery (except in the case of cardiogenic shock or persistence of ischemia after treatment of the culprit lesion). With respect to the treatment of the other arteries with lesions, a practical recommendation is to choose a “conservative strategy”, initially with medical treatment, and treatment of the other stenoses only when there are symptoms or induced ischemia. In the case of critical stenoses in segments proximal to major vessels, the strategy should be “staged” percutaneous or surgical revascularization in a later procedure (according to a multidisciplinary decision) during the hospital stay or within 1 month of the myocardial infarction.

The recommendation not to apply sex differences in the treatment is highly relevant, as is the fact that the guidelines stress the need to adjust the dose of antithrombotic therapy in elderly patients, women, and patients with renal failure; Table 18 of the guidelines is devoted to detailing the doses of these drugs for patients with creatinine clearance of <60 mL/min. The failure to make this adjustment is a common error that leads to a considerable increase in the incidence of bleeding.

MANAGEMENT DURING HOSPITALIZATION AND AT DISCHARGE

Logistic Questions, Risk Assessment, and Imaging Studies

The guidelines recommend that all hospitals that participate in the initial care of STEMI patients be equipped with a cardiac intensive care or coronary care unit. These units should be capable of providing specialized treatment to patients with acute coronary syndrome, arrhythmias, and heart failure, and their staff should be familiar with mechanical circulatory support systems, invasive and noninvasive hemodynamic monitoring, invasive and noninvasive respiratory monitoring and support, therapeutic hypothermia techniques, and renal support.

The management and duration of the hospital stay differ depending on patient risk. Although the levels of evidence are low, the guidelines recommend shortening the stay. For low-risk patients who undergo successful primary angioplasty, they consider same-day transfer to another center with no catheterization laboratory to be reasonable, although the level of recommendation is IIb C, and hospital discharge can be considered after 72 hours if adequate ambulatory follow-up is
possible. The question is, which patient is considered to be low-risk? Different indices (PAMI, Zwolle) can aid in very early risk stratification in patients who have undergone primary angioplasty.

The guidelines remark on the utility of the echocardiogram performed on admission in cases of uncertain diagnosis. This technique is also recommended to determine infarction size and left ventricular function, and to rule out complications. The use of magnetic resonance for these purposes is considered an alternative only when ultrasound is not feasible (IIb C).

The guidelines also point out that, once primary angioplasty has been performed and the coronary anatomy is known, the systematic assessment of ischemia prior to discharge is less important. These are level IA recommendations during the first 4 weeks to 6 weeks but only for patients with multivessel disease or in whom the possibility of revascularization of untreated vessels is being considered. Once again, the guidelines describe the strengths and weaknesses of each test, but still do not make their position clear in favor of a given modality. They are only categorical, and this is new, with regard to ruling out the utility of coronary computed tomography in this situation (III C).

For the viability study, they again enumerate the available techniques (nuclear imaging techniques, stress echocardiography, and magnetic resonance) and, because of the limited difference in the results obtained with each, leave it to the physician to decide which to employ.

**Treatment**

For the first time, a special section is devoted to the management of hyperglycemia. The guidelines point out the adverse prognostic implications of hyperglycemia and recommend diagnostic efforts in patients without known diabetes mellitus. The most important and novel message is summarized in the recommendation for the “strict, but not too strict” control of hyperglycemia, with emphasis on the need to avoid hypoglycemia. This strategy is condensed to maintaining blood glucose levels below 200 mg/dL (≤11 mmol/L) and over 90 mg/dL (<5 mmol/L) during the acute phase, much more permissive than the levels accepted up to now. The objectives are clearer than the strategy for achieving them, and insulin infusion, adjusted in accordance with the results of blood glucose monitoring, is recommended in some patients (IIa B). The use of glucose-insulin-potassium infusions is not indicated (III A).

The current guidelines present a fundamental difference with respect to the previous ones concerning the medical management of the acute and subacute phases and over the long term. The organization of the information is very clearly summarized in Table 22 of the guidelines.

All the treatment and secondary prevention measures should be initiated during the hospital stay with the aim of achieving maximum compliance after discharge. The relevant aspects are the emphasis on smoking cessation, with the recommendation that smoking cessation units be made available in every center, and the comments on benefits derived from cognitive behavioral assessment and therapy for stress management. It is important to point out that cardiac rehabilitation, so underutilized in Spain, continues to be a class IB indication.

One important change refers to arterial blood pressure control. Based on data from a retrospective analysis of the PROVE-IT TIMI 22 trial, the present guidelines are less strict than the previous ones and recommend that the target systolic blood pressure be under 140 mmHg, but not under 110 mmHg.

In lipid-lowering therapy, early intensive statin therapy is recommended for all STEMI patients, regardless of their cholesterol concentrations. On this occasion, the guidelines take a clear stand in favor of atorvastatin at a dose of 80 mg. The major recommendations concerning this matter and the differences with respect to the preceding guidelines are shown in Table 3 of the present article.

With regard to antiplatelet therapy, the administration of acetylsalicylic acid is not questioned, and the predominance of prasugrel and ticagrelor over clopidogrel has been mentioned in another section. The recommendations concerning the duration of antiplatelet therapy have not changed. The recommendation to maintain treatment with these agents for 12 months in patients who did not undergo stent placement (IIa C) may be debatable.

Doubts about the interaction between proton pump inhibitors and clopidogrel have been shelved because of the lack of evidence of its clinical significance, and the classical indications are maintained.

For anticoagulation therapy, more recent — and at the same time controversial — is the possibility of adding an oral factor Xa inhibitor (rivaroxaban) to acetylsalicylic acid and clopidogrel as adjunctive therapy in secondary prevention for patients at low bleeding risk (level IIb B recommendation), as tested in the ATLAS-ACS TIMI 51 trial. It is not known whether this strategy is superior to the combination of acetylsalicylic acid with prasugrel or ticagrelor. In addition to the fact that this indication has not yet been approved by the responsible agencies, a recent meta-analysis published after the guidelines had been released concludes that the new anticoagulant drugs show no net clinical benefit following acute coronary syndrome.

The guidelines continue to recommend (level IC) triple antiplatelet therapy (dual antiplatelet therapy and oral anticoagulation) for patients with atrial fibrillation and STEMI. This may need to be revised in the wake of the results of the WOEST trial, which could not be included in the guidelines as both were presented at the same time at the last ESC congress. Said study demonstrated greater benefit, including a reduction in mortality, compared with treatment with clopidogrel and oral anticoagulation versus the same treatment plus acetylsalicylic acid.

With respect to the remaining treatments, the postponement of beta-blockers is recommended until the patient is stabilized, except in the presence of hypertension or tachycardia and in the absence of smoking.
The indication for this technique for certain individual patients, given the extensive positive experience accumulated over the years. The decision should be made quite early, to avoid the development of irreversible multiple organ failure, and by cardiologists with extensive experience in the care of patients of this type. We expect that it will be possible to define the subgroups of patients who can benefit from intra-aortic balloon pump support in the near future. Further on, the guidelines refer to the stabilizing role of balloon counterpulsation in the mechanical complications of myocardial infarction (severe acute mitral regurgitation and ventricular septal defect).

The grade of recommendation of the use of a ventricular assist device in the management of refractory shock has also been reduced (from IIA C to IIB C), on the basis of a meta-analysis involving the Tandem Heart and Impella systems 2.5. These systems, which did not reduce 30-day mortality compared to balloon counterpulsation, may not be the most suitable devices at the present time.

The guidelines pay very little attention to ultrafiltration, although they support it with a considerable grade of recommendation (IIB) in cases of volume overload refractory to diuretics, especially in the presence of hyponatremia.

### Other Complications

There are no novel inputs with respect to arrhythmias. The guidelines insist on the need to carefully weigh the indication for coated stents in patients who should continue to receive anticoagulation therapy for atrial fibrillation. Nor are there important developments concerning the management of ventricular arrhythmias. The relationship between the development of malignant arrhythmias after the acute phase (24–48 hours) and a poor prognosis in patients with a markedly reduced LVEF should also be pointed out. Revascularization probably cannot prevent recurrence in these cases, even though the original arrhythmia may have been related to a transient ischemic attack. Under these circumstances, the placement of an implantable cardioverter-defibrillator is a IA recommendation.

The guidelines still fail to provide specific recommendations as to the best time for the surgical repair of postinfarction ventricular septal defects. Given the higher mortality rate associated with inferobasal defects, we feel that surgery should be considered earlier, even in the absence of confirmed evidence.

The incidence of ventricular mural thrombi has decreased significantly with improvements in reperfusion therapy. We have no recent data on the duration of anticoagulation therapy in these cases. The guidelines propose that, at the present time, taking into account the combination of dual antiplatelet therapy and anticoagulation, the latter can be discontinued earlier than 6 months if an imaging technique at 3 months demonstrates that the thrombus has disappeared.

### CONFLICTS OF INTEREST

Coordination of the Spanish nationwide clinical trial PLATO: Astra-Zeneca (MH), Clinical Committee endpoint: Eli-Lilly (AB).

Research grants awarded to the institution: Abbott-Vascular (AC), Boston Scientific (AC), GSK (MH), Medtronic (AC).

Consultancies: Abbott (MS), Astra-Zeneca (AB, JB, JL-S, MS, MH), Bayer (AB, AF, JB), Boheringer-Ingehelm (FW), Boston Scientific (IL), Chiesi (JB, FW), Cordis (MS), Daiichi-Sankyo (JB, AF, JL-S, FW), Eli-Lilly (AF, MS), Ferrer (AF), Medtronic (MS), MSD (AF), Rovi (AB), Sanofi (IL).

Educational reports and presentations: Abbott (AC, AF), Astra-Zeneca (AC, AF, JL-S, MH), Bayer (AC, JL-S, MP, MH), Biotronic (AC), Boheringer-Ingehelm (JL-S, FW, MH), Chiesi (AF, FW), Daiichi-Sankyo (AC,AF, JL-S, FW), Eli-Lilly (AF, MF), Ferrer (AC,AF), GSK (AF), Menarini (JL-S, MH), MSD (AF, FW), Roche (AF), Rovi (MH).
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