

## Indications of Treatment with Clopidogrel in the Guidelines of the Spanish Society of Cardiology for Unstable Angina/Non-ST-Segment Elevation Acute Myocardial Infarction

### To the Editor:

First of all, we would like to congratulate the authors of the Update of the Guidelines of the Spanish Society of Cardiology for Unstable Angina/Without ST-Segment Elevation Myocardial Infarction (ACSWESR)<sup>1</sup> for undertaking the enormous and difficult task that an update of this type entails with the thankless certainty that it will never reach total consensus. In this respect, I would like to remark on some points in the section on antiplatelet aggregation treatment, specifically the use of clopidogrel.

In the first place, a class I indication for clopidogrel is established in patients with ACSWESR of intermediate and low risk. In contrast, in high-risk patients the risk-benefit relation must be assessed when they receive treatment with glycoprotein IIb/IIIa inhibitors, since it is stated that the effects of the association are not known at present. Paradoxically, this lack of a clear position contrasts with the reality that the greatest benefit of clopidogrel in absolute terms is obtained in the high-risk group,<sup>2,3</sup> according to the TIMI risk classification. Clopidogrel reduces the absolute risk (AR) of death, infarction, or stroke by 4.8% (placebo, 20.7% vs clopidogrel, 15.9%;  $P=.003$ ), independent of any other type of coadjuvant treatment. In patients with low-to-intermediate risk, the reduction in AR, although significant, is lower in both, about 1.5%. The initial analysis of all the subgroups is consistent in the original article of the CURE study.<sup>4</sup> With regard to the risk, there is no foundation for affirming in the present guideline, as the results that will be developed more below show,<sup>2,3</sup> that the groups that benefited most were patients of intermediate and low risk.

Although no prospective study has evaluated primarily the benefit/risk of the association of clopidogrel and glycoprotein IIb/IIIa inhibitors, it cannot be claimed that the effects of this combination are not known. The patients of the TARGET trial<sup>5</sup> who received preliminary treatment (2-6 h before percutaneous revascularization) with 300 mg of clopidogrel, showed a significant reduction in the incidence of death, infarction, or urgent revascularization in the first 30 days in both the tirofiban group (7.2% vs 12.5%;  $P<.001$ ) and the abciximab group (5.8% vs 8.3%;  $P=.026$ ). Likewise, in the EPISTENT study,<sup>6</sup> previous treatment with ticlopidine of patients who were treated with abciximab reduced the need for revascularization in the first year (RR, 0.62;  $P=.01$ ). With regard to the safety of the association, in the PCI-CURE trial,<sup>7</sup> clopidogrel did not increase the incidence of major hemorrhage in patients that received a glycoprotein

IIb/IIIa inhibitor: 2.2% in the clopidogrel group versus 2.2% in the placebo group. Similarly, in the above-mentioned EPISTENT study,<sup>6</sup> the percentage of hemorrhage was identical to that seen with the association of abciximab and ticlopidine: 1.5% vs 1.5% with abciximab alone. In other studies, the combination of clopidogrel or ticlopidine with different glycoprotein IIb/IIIa antagonists has not increased average bleeding time with respect to that observed with glycoprotein IIb/IIIa antagonists alone.<sup>5,8,9</sup>

It is also surprising that after admitting the benefit of previous treatment with clopidogrel in patients treated with percutaneous revascularization, its indication is limited to class I under the assumption that the patients have not been treated with glycoprotein IIb/IIIa inhibitors or in every case in the first 30 days after angioplasty. The evidence is clear: the greatest benefit of clopidogrel is obtained by administering it at least 2 h before revascularization<sup>5,7</sup> rather than during the intervention or afterward. On the other hand, PCI often cannot be performed in the first 24 h, which thus eliminates the early benefit of clopidogrel<sup>14</sup> in these high-risk patients.

In my opinion, the indication for clopidogrel treatment in patients with high-risk ACSWESR should be class I, as well as for previous treatment in the case of intended PCI. This view is consistent with ACSWESR guidelines published recently by the ACC/AHA.<sup>10</sup>

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### REFERENCES

- López Bescos L, Arós F, Lidón RM, Cequier A, Bueno H, Alonso JJ, et al. Actualización (2002) de las Guías de Práctica Clínica de la Sociedad Española de Cardiología en angina inestable/infarto sin elevación del segmento ST. *Rev Esp Cardiol* 2002;55:631-42.
- Yusuf S, Mehta SR. Treatment of acute coronary syndromes [carta]. *N Engl J Med* 2002;346:207-8.
- Budaj AJ, Yusuf S, Mehta S, Fox KAA, Tognoni G, Zhao F et al. Benefit of clopidogrel in patients with acute coronary syndromes without st-segment elevation (ACS) in various risk group. *J Am Coll Cardiol* 2002;39 (Suppl B):441B.
- Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without st-segment elevation. the clopidogrel in unstable angina to prevent recurrent events trial investigators. *N Engl J Med* 2001;345:494-502.
- Topol EJ, Moliterno DJ, Hermann HC, Powers ER, Grines CL, Cohen DJ, et al, for the TARGET Investigators. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001;344:1888-94.
- Steinhuyl SR, Ellis SG, Wolski K, Lincoff AM, Topol EJ for the EPISTENT Investigators. ticlopidine pretreatment before coronary stenting is associated with sustained decrease in adverse cardiac events. Data from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) Trial. *Circulation* 2001;103:1403-9.

7. Mehta SR, Yusuf S, Peters RJG, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pre-treatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; 358:527-33.
8. The ESPRIT Investigators. Novel dosing regimen of eptifibatid in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 2000;356:2037-44.
9. Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. *Circulation* 2001;104:539-43.
10. ACC/AHA 2002 Guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on practice Guidelines. Disponible en: [www.acc.org/www.americanheart.org](http://www.acc.org/www.americanheart.org).

## Response

### To the Editor:

Thank you for the letter from Dr. V. Valentín, who remarks on one of the points for which it was difficult to reach a consensus in the update of the Guidelines.<sup>1</sup>

As is well known, the recommendations of the Clinical Practice Guidelines are established in a given moment, using the knowledge available at that time. They reflect the assessment by the members of the writing committee of the published data and their final consensus regarding different criteria, thus resulting in the recommendation most acceptable for all.

In order to reach this point, it is necessary to travel a road that is often complicated.

The first of the factors involved is the interpretation of data. Although it is easy to evaluate the statistical significance of the results of clinical trials through the *P* value, it is much more complex to evaluate clinical significance. This is particularly necessary when dealing with a single study (CURE<sup>2</sup>). The relative importance of the different endpoints (death, infarction, CVA) versus the overall objective must be analyzed.<sup>3</sup> The impact on different subgroups of risk and the definition of events (in this case, the definition of infarction) also condition clinical repercussion.

As Dr. Valentín knows very well, the data from trials sometimes change between the first communication and later publications. When the guidelines were drafted, published data from the CURE study<sup>2</sup> supported the effectiveness of clopidogrel in groups of intermediate and low risk, but the benefit in the high-risk group (18.0% with placebo versus

16.3% with clopidogrel; a benefit of 1.7% in absolute terms, 9.4% in relative terms) was not significant. The unit line exceeded confidence limits so this recommendation was not included as class I. The references cited in your letter had not been published when the manuscript was written.

The most important complication associated with the use of clopidogrel in ACS is hemorrhage, particularly in high-risk patients undergoing surgery. Percutaneous coronary interventions (PCI)<sup>4</sup> have their clearest indication in association with the use of a glycoprotein IIb/IIIa inhibitor.<sup>5</sup> We do not know of any study that has directly assessed the result of simultaneous use of acetylsalicylic acid, heparin, glycoprotein IIb/IIIa inhibitor, and clopidogrel in these patients before and during PCI, but it seems reasonable to think that this combination can increase the risk of hemorrhage if used systematically. This was the second reason for not including clopidogrel as class I in this group of patients in which glycoprotein IIb/IIIa is recommended.<sup>1</sup>

Surely in the near future, what was known at the time that the update of the guidelines was written will be modified by the appearance of new findings that will require a new review of these recommendations due to the appearance of clear and convincing evidence.

Lorenzo López Bescós and Fernando Arós  
on behalf of the Writing Committee Update  
2000 of Clinical Practice Guidelines in  
Acute Coronary Syndrome of the Spanish  
Society of Cardiology.

### REFERENCES

1. López Bescós L, Aros Borau F, Lidon Corbi RM, Cequier Fillat A, Bueno H, Alonso JJ, et al. Actualización de las Guías de Práctica Clínica de la Sociedad Española de Cardiología en Angina Inestable/Infarto sin elevación del segmento ST. *Rev Esp Cardiol* 2002; 55:631-42.
2. The clopidogrel in unstable angina to prevent recurrent events trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST segment elevation. *N Engl J Med* 2001;345:494-502.
3. Khot UN, Nissen ST. Is CURE a cure for acute coronary syndromes? Statistical versus clinical significance. *J Am Coll Cardiol* 2002;40:218-9.
4. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with glycoprotein IIb-IIIa inhibitor tirofiban. *N Engl J Med* 2001; 344:1879-87.
5. Kleiman NS, Lincoff AM, Flaker GC, Pieper KS, Wilcox RG, Berdan LG, et al. Early percutaneous coronary intervention, platelet inhibition with eptafibatid, and clinical outcomes in patients with acute coronary syndromes. *Circulation* 2000;101:751-7.