Clopidogrel in Acute Coronary Syndromes with Non-ST Elevation

To the Editor:

I have read with great interest the editorial regarding the clinical repercussions of the CURE study.[1,2] I believe it was an excellent description of the study and the questions it poses, but I would like to make some observations on the article.

In the first place, my attention it drawn to the extremely conservative management of the patients included in the study, which could have an influence on the benefits which were observed. In spite of the fact that one-third of the patients were categorized as high risk and another third as intermediate risk, only 21.8% underwent revascularization during admission (13.8% with angioplasty and 8% with surgery). I do not know whether managing the patients at risk in accordance with current recommendations[3] (use of glucoprotein IIb/IIIa antagonists and revascularization) would have provided the same benefit as that observed.

In the second place, the convenience of prolonged treatment, as is mentioned in some of the author´s opinions, should be clarified. In the low risk group more precise data is needed regarding the cost to efficacy ratio: 62 patients had to be treated in order to avoid an event; this treatment is costly and has a certain risk of hemorrhage. On the other hand, the results from the PCI-CURE study[4] demonstrated that the benefit obtained in patients undergoing percutaneous revascularization occurred during the pre-angioplasty period and in the 30 days post-angioplasty. After 30 days, there were no significant differences in the presence of cardiovascular mortality and myocardial infarct (3.6% placebo group and 3.1% in the clopidogrel group). In these patients, therefore treatment prior to intervention and 30 days following could be sufficient.

In the third place, my attention is drawn to the tone of the article purported to be an editorial in the REVISTA ESPAÑOLA DE CARDIOLOGÍA. For example, the following paragraph is a literal quote: «The final conclusion of the CURE study is that clopidogrel significantly reduces the risk of cardiovascular death, myocardial infarct, and cerebrovascular accident, a benefit which more than compensates for excessive bleeding.» The authors of the study expressed these conclusions: «The platelet aggregation inhibitor clopidogrel has important benefits in patients with acute coronary syndromes without ST-segment elevation. Nevertheless, the risk of significant hemorrhage was increased in those treated with clopidogrel.»

Finally, I would like to say that it would be a good idea is those authors with a commercial involvement would indicate what kind of relationship they have or had with the pharmaceutical industry that selling these products.

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Response

To the Editor:

I have read with interest the letter from Dr. Berjón concerning my editorial «Clopidogrel in acute coronary syndrome without ST-segment elevation. Clinical repercussions of the CURE study.»[1] I appreciate your interesting comments, although I disagree with some of them and would like to make a few points.

As was mentioned in the discussion of the original article[2] and in my editorial, the study did not recommend early intervention, as its clinical efficacy had not been demonstrated either at the time of the study design or during its later development. This could have led to an immediate interruption in the medication regimen in the study and to the use of clopidogrel in a higher percentage of patients. Nevertheless, if the physician thought that a patient included in the study required coronary angiography and needed for revascularization, the study medication was suspended temporarily and the patient received ticlopidine or clopidogrel treatment. In fact, during the study 21.2% of patients underwent angioplasty and 16.5% cardiac surgery. As is also mentioned in my editorial, it is only recently that the clinical efficacy of early angioplasty in association with Gp IIb/IIIa antagonists in high-risk patients has been demonstrated.[3] Attempting to quantify the exact benefit of clopidogrel combined with early intervention and Gp IIb/IIIa blockers would be little more than a speculative analysis with the data currently available. Nevertheless, there is clear indirect evidence of their usefulness in this context. In the first place, the simple combination of aspirin and clopidogrel, regardless of any additional treatment and with or without intervention, reduces by 27% the relative risk of death, infarct, or cerebrovascular accident in the high risk group ($P<.004$)[4], a decrease of 38 major events for

every 1000 patients treated. On the other hand, 85% of the cases who underwent angioplasty in the TACTICS[3] study also had a coronary stent implanted, which is a class I indication for treatment with clopidogrel. Finally, also in the field of early intervention, the association of ticlopidine with abciximab has shown a significant reduction in the need for revascularization at 1 year in the EPISTENT study,[5] while those previously treated with clopidogrel improved significantly at 30 days, both in patients who received abciximab and those who received tirofiban, in the TARGET study.[6]

At no time was the need for long-term treatment with clopidogrel in low-risk patients confirmed, but rather that future studies of cost to efficacy ratio and long-term follow-up need to be performed, «...it would be logical to use long-term clopidogrel in medium and high risk patients and weigh the risk to benefit ratio in low risk patients.» In any case, I believe that we should not dismiss the fact that a decrease of 16 major events (death, infarct, or cerebrovascular accident) in every 1000 patients occurred in the low risk group (relative risk 0.71; *P*<.04)4, which is greater than the 10 deaths or infarcts which resulted with the Gp IIb/IIIa antagonists in the acute coronary syndrome group–independent of the risk–and without intervention (relative risk 0.91; *P*=.015)7. I also did not mention in my editorial the results of the PCI-CURE study,[8] but I agree with Dr. Berjón´s comments that after 30 days post-angioplasty, there is no significant statistical difference in the incidence of cardiac mortality or myocardial infarction (3.1% in the clopidogrel group vs 3.9% in the placebo group; relative risk 0.79; 95% confidence interval [CI], 0.53-1.20). In any case, I believe we are dealing with a partial sample from the CURE study (approximately 21% of the population) which could lessen the statistical significance of same. On the other hand, the trend is identical to that observed in the remaining subgroups of the CURE study, and when the Kaplan-Meier cumulative risk curve is analyzed (seen in Figure 3)[8], there is a continuous separation of both curves throughout the year, with the clopidogrel outcome being more favorable; this finding is more accentuated and persistent after 200 days.

In effect, the final conclusion of the CURE study which is reproduced in my editorial is not a literal translation of the contents of the original article, but a statement that the benefits of the combination of aspirin and clopidogrel more than compensates for excessive hemorrhaging that was expressed by the principal authors as a conclusion in the public presentation of the preliminary results and on other later occasions, the last of these being a letter to the editor.[4] In the latter, an analysis of the risk to benefit ratio which included the incidence of hemorrhage in the initial objective made up of mortality, infarct and ictus show a clear benefit of clopidogrel vs placebo (relative risk 0.84; 95% CI, 0.76-0,93; *P*=.001)[4]. On the other hand, the opinion is put forth that transfusion of 2 red blood cell concentrates (the criteria for a major hemorrhage in the study) is not clinically equivalent to death, infarct, or cerebrovascular accident. Finally, in the same vein, consider the recent proposal for modification of the treatment guidelines for acute cardiac syndrome without ST-segment elevation formulated by Braunwald[9], which in the case of clopidogrel constitutes a class I indication (A evidence level): *a)* in all patients with acute coronary syndrome without ST-segment elevation for 9 months, and *b)* prior to and during the 30 days following angioplasty; class I indication (B evidence level): during the 9 months following percutaneous coronary intervention.

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