Low-Dose of Aspirin, Gastroprotection and *Helicobacter Pylori* Erradication

To the Editor:

The editorial by Lanas y Ferrández[1] on the use of gastric protection in patients on low-dose aspirin therapy that recently appeared in the REVISTA is very interesting. The significant morbidity from cardiovascular disease in Western societies, the fact that aspirin has been shown to be effective in the prevention of coronary or cerebrovascular events, together with the authors´ experience on this subject makes the article of great interest. Nevertheless, we would like to make some comments on the contents of this editorial. We believe that until more studies are done, we must take into account other risk factors for the develop of complications in patients on aspirin therapy who have a history of ulcerative disease or digestive hemorrhage, who are taking non-steroidal anti-inflammatory medication (NSAIDs) in conjunction with aspirin, and who are infected with *Helicobacter pylori*. Age of 60 years or greater and corticoid or anticoagulant therapy are risk factors that must be taken into account when adding a protective agent for the gastric mucosa, as is advised in patients treated with classic NSAIDs.[2]

On the other hand, although we agree with the recommendation to use proton pump inhibitors as preventative measure for patients on chronic aspirin therapy, we do not think it accurate to conclude that the eradication of *H. pylori* is recommended in these patients. Studies on the subjects on the use of NSAIDs at the usual doses are controversial, and it has even been suggested that *H. pylori* may have a protective effect against lesions caused by NSAIDs. In the recommendations of the Conferencia Española de Consenso[3] the inadvisability of eradicating the bacteria in asymptomatic patients taking NSAIDs was mentioned, and it was also recommended that in the presence of a concomitant history of ulcer, the bacteria should be protected with a proton pump inhibitor, and to wait until NSAIDs are no longer being taken before eradicating the bacteria. As noted in the editorial, there are few current studies on the use of low-dose aspirin, with few patients, short followup periods; and some of which are only abstracts and report conflicting results.[1,4,5] Many questions are raised by accepting the recommendation to eliminate *H. pylori* in these patients: would we have to know if a patient is infected before prescribing low-dose aspirin? Should we only check if the patient has a history of ulcers? What diagnostic tests would have to be performed a breath test, serology testing for the bacteria, or endoscopy, biopsy, and urine tests? Should the eradication of the bacteria be confirmed later? Therefore, we think that it is premature and excessive to advise this course given current contraindications and without it being established which patients are involved, and when, and how it should be carried out.

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Response

To the Editor:

We appreciate the interest of Drs. Zambrana, Rodríguez-González, and Puente in our editorial published in the REVISTA.[1] Making practical recommendations is difficult when available scientific evidence is not abundant or even existent, and does not even answer specific clinician questions. In spite of this, we believe that the available studies support the ideas and concepts contained in the editorial.

We would like to point out that although acetylsalicylic acid is a NSAID, its therapeutic use is limited to low doses for preventing occlusive vascular disease. Data obtained when using NSAIDs in anti-inflammatory or analgesic doses are not entirely applicable to low-dose aspirin. The data collected on the subject confirm and stress varying degrees of risk.

At the moment, therefore, there are no studies that show age greater than 60 years or the use of corticosteroids increases the risk of hemorrhage in patients who take low-dose aspirin. On the other hand, there are data that indicate that a history of ulcer or the concomitant use of NSAIDS significantly increases the risk of hemorrhage in these patients.[2-5] We must therefore limit our recommendations to those which have a scientific basis, despite the fact that it may be reasonable to assume that higher age implies greater risk. To put the limit at 60 years seems appropriate in light of the currently available information. Similarly, data on the risk with concomitant use of anticoagulants or the presence of concomitant serious illnesses is scarce, or even nonexistent. Clinical logic would dictate that although the risk is low, developing a hemorrhage can be fatal, and therefore it seems reasonable, even imperative, to add a gastroprotective agent.

The most controversial subject seems to be that of the role of *Helicobacter pylori* infection. The literature, to be sure (including the recommendations of panels of experts which one of the authors of this article served on)[6] is confusing. The new data, however, indicates that *H. pylori* is a risk factor for all patients who take NSAIDs.[7] There appears to be a greater consensus when reviewing the information on low-dose aspirin; currently, few researchers doubt that *H. pylori* is a risk factor for patients taking that medication at that dose.[2-5] This means that infection must be eradicated or tested for in all patients who take low-dose aspirin. Enacting gastroprotective measures in a patient who takes NSAIDS or low-dose aspirin requires evaluation of the risk factors present. If they do exist, especially in those who have an increased risk of hemorrhage (history of ulcer or hemorrhage, concomitantly taking NSAIDs), administering a proton pump inhibitor would likely be sufficient to significantly reduce the risk of hemorrhage. Nevertheless, a history of ulcer or previous complications favors eradication of *H. pylori* because, in most cases, 1 week of antibiotic treatment reduces the risk of upper digestive system hemorrhage even more (especially in the case of duodenal ulcer). It is very possible that future studies will indicate, from the risk/benefit perspective, that subpopulations require eradication of *H. pylori* as the only therapeutic measure. At this time, however, the most reasonable practical suggestion is to prescribe a proton pump inhibitor in the presence of risk factors and also to eradicate *H. pylori* if there is evidence of previous gastroduodenal ulcer. At present, this is the usual practice in gastroenterology practices in our country. The best and least difficult test to confirm the presence or absence of infection is a breath test, but other tests, including fecal testing, are also perfectly valid.

We understand that dealing with an infection like *H. pylori* for medical professionals not familiar with the problem results in inconsistencies in patient management, but gastroenterologists have learned the enormous benefits reported from its elimination in patients with ulcerous diathesis.

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Homocysteine and Coronary Artery Disease

To the Editor:

We read with great interest the article entitled «Total Concentrations of Plasma Homocysteine in Puerto Rican Patients With Ischemic Heart Disease» by Rodriguo et al.[1] published in the December issue of the REVISTA. Given the enormous pervasiveness of the subject, we would like to make some comments.

Firstly, in the Introduction, the authors comment that in Spain studies of ischemic heart disease have been focused more on the theory of the increase in cholesterol, and that there are no studies of homocysteine values in this population. There is a Spanish study[2] on this topic that reported that 26% of patients with heart disease proved to have hyper-homocysteinemia.

Secondly, the authors did not determine vitamin B_6, B_{12}, and folic acid values in cases in which deficits thereof could be a nutritional cause of hyperhomocysteinemia. It has been suggested that

approximately 60% of hyperhomocysteinemia is due to inadequate levels of 1 or more of these vitamins in the blood.[3] Similarly, they did not comment on the dietary habits and condition of the study population, and this is probably why there was no finding of an association between heart disease and homocysteine concentration as a side effect of long- and short-term dietary variations.[4] Various retrospective and prospective studies have shown the possibility that a load test would improve the ability of a fasting homocysteine measurement.[5] to predict the risk of heart disease.

Thirdly, the results are expressed in an unclear manner. In Table 2, the distribution of homocysteine is grouped by age, sex, smoking habits, diabetes and arterial hypertension. The authors express homocysteine concentrations for the entire population, instead of placing them in 2 categories—those with normal coronary arteries (n=10) and those that had some degree of occlusion (n=60). In Table 3, which lists the univariate and multivariate models for the different parameters that can accelerate artery occlusion, we would like to note that recent studies have concluded that using logic regression analysis in the context of small samples requires the use of exact tests (for example, the Cytel software statistical program[6]). The exact test, as is well known, decreases type 1 errors associated with the conflicting theories such as those described in the study. Especially when multivariate models are used in clinical studies, the precaution must be taken to maintain a balance between the number of predictors and the number of patients in the sample. In this study, there are 70 patients with a preliminary diagnosis of heart disease with only 10 in the control group (normal coronary arteries) making it impossible to use more than 1 or 2 variables at the most in prediction for or classification of the patients.

Fourthly, the sample size that the authors present is 60 patients (all with some degree of arterial occlusion) and 10 controls (normal coronary arteries). It is well known that it is complicated to determine with coronary angiography that controls are without ischemic heart disease; nevertheless, the control group might be amplified with patients who have a negative stress test. This contradicts the conclusions of the study since the impossibility of reaching conclusions is in the actual study design itself–it lacks sufficient statistical power.

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Response

To the Editor:

We appreciate the interest of our colleagues in the Canary Islands in the article presented by our group in Puerto Rico regarding the contentious subject of homocysteine plasma levels and heart disease. The study we are performing at the Puerto Rico and Caribbean Cardiovascular Center is still in process and results in the article were the preliminary analyses of the patients on whom we had complete data. At the time of writing this reply, we have accumulated data on a total of 155 patients, of which 19 are controls who have no ischemic cardiopathy. The results in these additional patients have in no way altered the values or trends discussed in our original article. We saw no correlation between homocysteine plasma values and the progressive categories and coronary angiography results. We are still recruiting patients for the study and hope to publish findings on a larger group of patients in the near future. Results for vitamin B_6, B_{12}, and folic acid levels are being obtained at this time and will also be published in the near future, as was the case in our recently published study on a colony of Rhesus monkeys *(Mucaca mulatta).*[1] We regret that we did not identify the homocysteine studies performed in Spain, but we limited our search to the REVISTA ESPANOLA DE CARDIOLOGÍA, where we could not find a single published article. We would like to comment, nevertheless, that in the study by Fernandez-Miranda et al,[2] there was a difference in homocysteine plasma values between patients with coronary disease and the control group (11.7 μM vs 8.4 μM; $P<.001$). It should

be noted that the homocysteine plasma concentrations in the controls in the study are much lower than those reported in other studies around the world.[3] It is of note that in studies in which homocysteine plasma concentrations and coronary angiography have been performed in control groups, no correlation has been found between hyperhomocysteinemia and ischemic heart disease.[4] More notable still is that prospective studies have shown no such relationship. We understand that the problem of ischemic cardiopathy is multivariate and complex, and the relationship between factors is more important than a single isolated factor.

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