Despite the difficulties in establishing causality due to multiple factors that could be related to drug-eluting or bare-metal stent thrombosis, we think the following considerations should be taken into account.

A test formulation is considered bioequivalent to a reference medication if the 90% confidence interval (CI) of the geometric mean for the area under the curve (AUC) and maximum plasma concentration ($C_{\text{max}}$) is between 80% and 125%. In the case of the polypill approved in Spain, a bioequivalence trial was conducted. The 90% CI of the geometric means for both AUC and $C_{\text{max}}$ were within these limits and so bioequivalence was demonstrated according to the accepted criterion. Specifically, in the case of acetylsalicylic acid, the 90% CIs were 96.92%-104.47% for AUC and 84.51%-95.78% for $C_{\text{max}}$.

These results, which demonstrate bioequivalence for acetylsalicylic acid in the polypill compared to separate pills, suggest the polypill can be used in the same indications as acetylsalicylic acid, in this case, as a strategy for secondary prevention in patients with ischemic heart disease, regardless of the clinical presentation (after acute coronary syndrome or in chronic phase) and treatment (after percutaneous revascularization or surgery or in patients without revascularization). In different clinical trials with polypills in patients with ischemic heart disease, which include the FOCUS study, there was no evidence of increased ischemic complications compared with the separate components, although that study excluded patients with drug-releasing stents. These patients were, however, included in the SECURE (Secondary Prevention of Cardiovascular Disease in the Elderly Trial, NCT 02596126) study that randomized patients over 65 years of age with recent myocardial infarction to the polypill or the individual components.

**CONFLICTS OF INTEREST**

J.R. Gonzalez-Juanatey is a speaker for Ferrer International.

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**Insufficient Lipid Control in Patients With Coronary Artery Disease: An Unresolved Problem**

**Insuficiente control de parámetros lipídicos en pacientes con enfermedad coronaria: un problema por resolver**

To the Editor,

We have read with interest the article published by Galve et al. in Revista Española de Cardiología concerning the degree of lipid control in patients with coronary artery disease. The authors report an observational study in which they found that poor control of low-density lipoprotein cholesterol (LDL-C) levels has been reported constantly in recent years, a situation that we believe should prompt reflection. There is a great deal of scientific evidence that associates LDL-C levels with the development of new cardiovascular events in patients with coronary artery disease. This evidence has led the current clinical practice guidelines to consider the achievement of LDL-C levels < 70 mg/dL in these patients to be a class I recommendation. However, barely 1 in 4 patients achieves that therapeutic target, even with lipid-lowering therapy. In the treatment of patients with coronary artery disease, other therapeutic strategies with a class I recommendation—primary angioplasty or the use of dual antiplatelet therapy—reach much higher rates of compliance with therapeutic goals. We believe this could be due to the difference in the time it takes for the benefit to be observed; whereas the benefit observed with percutaneous treatment is practically immediate, lipid control requires proper treatment adherence for its beneficial effect on mortality and morbidity to become apparent. Although the achievement of optimal LDL-C levels reduces cardiovascular mortality by an additional 20%, Galve et al. found that lipid-lowering therapy was modified in only 26% of patients with poor LDL-C control. This finding suggests that, in general, scant attention is paid to this very important parameter of secondary prevention. In addition, another factor associated with poor LDL-C control may be individual variation in the response to lipid-lowering therapy. A recent communication reported that at least half of the patients treated with high-intensity statin therapy achieve a reduction in LDL-C > 50%, but that 10% of those patients show no change or even an increase in LDL-C levels. Given the resulting prognostic benefit, it is essential to optimize LDL-C concentrations in most patients with coronary artery disease, a fact that has been reflected in the recent document of the Spanish Society of Cardiology dealing with quality indicators in cardiology. On the other hand, subtilisin/kexin 9 inhibitors, with a presumed lower variation among the responses of the different groups and a reduction in LDL-C > 60% compared with baseline, could help to improve lipid control. The inclusion of these patients in cardiac rehabilitation programs helps to optimize secondary prevention parameters and, thus, to reduce morbidity and mortality rates. This strategy is categorized as a class II recommendation in recent guidelines on cardiovascular disease prevention. For this reason, it should be applied in most of our patients.

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Insufficient Lipid Control in Patients With Coronary Artery Disease: An Unresolved Problem. Response

To the Editor,

We thank Renilla et al. for their comments regarding our article on insufficient lipid control in patients with coronary artery disease,¹ and we must agree with the majority of their comments and reflections.

The results of our study may appear somewhat disheartening, with good control [low-density lipoprotein (LDL] < 70 mg/dL] being achieved in only 26% of patients with coronary artery disease in Spain. However, we must bear in mind that this is an improvement: 95% of patients currently receive lipid-lowering therapy and 45% receive high-intensity lipid-lowering therapy; not too long ago, in 2006, 31% received no statins and only 10% received high-intensity therapy.² It is true that there is a lack of awareness among professionals regarding the appropriate measures to avoid clinical inertia, but it is equally true that with a purely statin-based treatment, such ambitious targets are unlikely to be met. It is known that LDL-cholesterol is significantly reduced when treatment with statins is started (up to 50% if started directly on a high-intensity statin), but dose increases cause only small percentage decreases (7% to 9% when the dose is doubled); when ezetimibe is added, this can be up to 20%.³ Therefore, if high LDL values in patients on treatment are used as a means of evaluation, the target values will never be met. Renilla et al. also raised the point of the variable response to lipid-lowering therapy; regarding this, one of the most notable aspects of the REPAR study at one-year follow-up (data as yet unpublished) is that some of the patients that were initially well-controlled (LDL-cholesterol < 70 mg/dL) at the start of the study were no longer well-controlled at follow-up, despite unchanged lipid-lowering therapy. Renilla et al. highlight the opportunity presented by the incorporation of PCSK9 inhibitors to the therapeutic arsenal. However, these drugs come with several limitations, as initial government guidelines⁴ indicate that these will be funded only for patients already on maximum treatment doses and with LDL-cholesterol levels > 100 mg/dL. This leaves a group of patients with LDL-cholesterol between 70 mg/dL and 100 mg/dL, which contains most of the patients who are already on treatment but are not well controlled, in a limbo with no therapeutic solution.

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