Rev Esp Cardiol. 2016;69(10):995–999

Letters to the Editor

Consensus Document on Polypill and Secondary Prevention. Does It Include Patients With Stents?

***Documento de consenso del policomprimido en prevención secundaria. ¿Incluye a los pacientes con* stent?**

To the Editor,

We have read with interest the consensus document on the use of the polypill[1] and the editorial by González-Juanatey et al.[2] The authors should be congratulated for their initiative in producing a document that helps to increase our knowledge of this therapy and, moreover, defines the situations in which its use can be beneficial. The European Society of Cardiology indicates that reducing the frequency of administration is the most effective way to improve treatment adherence, and it reportedly could reduce cardiovascular events by 75%. However, in our opinion, this document does not deal with an aspect that we consider of vital importance in secondary prevention. Both the consensus document and the editorial underline the need to control hypertension and cholesterol, stressing high-risk patients, but make no mention of patients with coronary stents. We feel that they should include some comment on this subject, especially concerning drug-eluting stents, therapeutic devices used in most patients with acute coronary syndrome,[3] since we consider that the currently available data are insufficient.

In our center, there was a recent case of very late definite thrombosis of an everolimus stent, implanted 16 months earlier in a patient who, 1 year after the procedure, had been taken off clopidogrel and aspirin in their individual forms and had started polypill therapy.[4] Although an absolute cause and effect relationship cannot be established, we believe that this case should prompt reflection. We wish to highlight that we have found no data on patients with stents either in the patient information leaflet on the drug or in studies conducted to date, with the exception of a study by Castellano et al.[5] who excluded patients during the first year after implantation of a drug-eluting stent. However, that report does not mention the number or percentage of patients with bare-metal stents included during the first year after implantation or of those with drug-eluting stents beyond the first 12 months. Although the polypill undoubtedly contributes a great deal to improving adherence, some authors have indicated that it may not reach the same level of efficacy as its 2 components separately, and that the bioavailability, pharmacokinetics, and possible interactions should be tested in each of the formulations. Moreover, although the effects of the components are assumed to be additive, this assumption should be demonstrated with studies performed with each formulation.[6] This could be particularly important for high-risk patients. The present consensus document mentions patients at higher risk, but only to refer to the possible lack of hypercholesterolemia and hypertension control, when we believe that the most important aspect of the risk and, moreover, over a much shorter term, is the possibility of stent thrombosis. For all these reasons, until studies are conducted that include patients with drug-eluting stents in the first year after implantation, we consider, on the one hand, that the use of the polypill from the time of hospital discharge, as proposed, should not be recommended and, on the other hand, that some comment on the absence of published data on their use in this specific type of patients should be included.

Iñigo Lozano,* José M. Vegas, Juan Rondán, and Eduardo Segovia

Servicio de Cardiología, Hospital de Cabueñes, Gijón, Asturias, Spain

* Corresponding author:
E-mail address: inigo.lozano@gmail.com (I. Lozano).

Available online 17 August 2016

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Consensus Document on Polypill and Secondary Prevention. Does It Include Patients With Stents? Response

Documento de consenso del policomprimido en prevención secundaria. ¿Incluye a los pacientes con* stent? *Respuesta

To the Editor,

We appreciate the comments by Lozano et al.[1] on the consensus document and editorial published in the *Revista Española de Cardiología* about the use of the polypill.[2] This consensus document made some recommendations based on current evidence and, when no evidence was available, the consensus opinion of the authors. As a possible use of the polypill, the consensus mentions patients with a recent coronary event who, given their characteristics, may have a low adherence to therapy. Lozano et al.[1] question basic aspects of clinical use of the polypill: bioequivalence of acetylsalicylic acid and the results with this new therapeutic strategy after thrombosis in patients with recent coronary stent placement, particularly, when a new drug-eluting stent was used.

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_{max}) is between 80% and 125%. In the case of the polypill approved in Spain, a bioequivelence trial was conducted. The 90% CI of the geometric means for both AUC and C_{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_{max}.[3]

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,[4] 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.

José R. González-Juanatey, on behalf of the authors of the Consensus Document on Clinical Use of the Polypill in Secondary Prevention

Servicio de Cardiología y UCC, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain

E-mail address: jose.ramon.gonzalez.juanatey@sergas.es

Available online 9 September 2016

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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.[1] 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[2] to consider the achievement of LDL-C levels < 70 mg/dL in these patients to be a class Ia recommendation. However, barely 1 in 4 patients achieves that therapeutic target, even with lipid-lowering therapy.[1,3,4] 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%,[5] Galve et al.[1] 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.[6] 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.[7] 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,[8] 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 Ia recommendation in recent guidelines on cardiovascular disease prevention.[2] For this reason, it should be applied in most of our patients.

Alfredo Renilla,* Sergio Hevia, and Vicente Barriales

Unidad de Rehabilitación Cardiaca y Prevención Secundaria, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain

* Corresponding author:
E-mail address: dr.renilla@gmail.com (A. Renilla).

Available online 17 August 2016