

Editorial

A Step Ahead in Secondary Prevention of Cardiovascular Risk. Consensus Document on Clinical Use of the Polypill



Un paso más allá en la prevención secundaria del riesgo cardiovascular. Documento de consenso del uso clínico del policomprimido

José Ramón González-Juanatey,^{a,*} José María Mostaza,^b José María Lobos,^c Benjamín Abarca,^d and José Luis Llisterri^e

^aSociedad Española de Cardiología, Madrid, Spain

^bSociedad Española de Medicina Interna, Madrid, Spain

^cSociedad Española de Medicina de Familia y Comunitaria, Barcelona, Spain

^dSociedad Española de Médicos Generales y de Familia, Madrid, Spain

^eSociedad Española de Médicos de Atención Primaria, Madrid, Spain

Article history:

Available online 6 April 2016

INTRODUCTION

Inadequate adherence to prescribed therapies is a major barrier in secondary prevention of cardiovascular disease (CVD) and in fulfilling the recommendations related to health care quality indicators.¹ Several factors may contribute to this suboptimal adherence: the chronic and sometimes oligosymptomatic nature of CVD, copayment for medications, complex therapeutic regimens, and a lack of related educational programs for professionals and patients.²

The consequence of poor adherence to therapy³ would most likely be an increase in major cardiovascular (CV) complications, which could lead to higher mortality, poorer quality of life in surviving patients, a greater health care burden, and cost increases resulting from complications and hospitalizations.

Several measures have been found to improve therapy adherence, such as copayment reductions, automatic reminders, mail order pharmacies, assessment by a health professional, and fixed-dose combination therapy.⁴ Simplification of therapeutic regimens by fixed-dose combinations is a complementary strategy to improve treatment adherence in several types of diseases, and is favorably received by patients.⁵ In addition, fixed-dose combination therapy enables reductions in production and distribution costs, making it a less expensive option.²

The polypill for secondary CVD prevention is the first fixed-dose combination approved in Europe as simplification therapy for adult patients who are well-controlled when the individual components of the pill are administered separately at equivalent therapeutic doses.⁶ The polypill is presented in the form of capsules containing 3 active pharmaceutical components: 100 mg of aspirin, 20 mg of atorvastatin, and 2.5, 5, or 10 mg of ramipril. A presentation form containing 40 mg of atorvastatin is currently

under development. In Spain, the cost of the polypill is equivalent to the sum of the cost of the 3 generic components.

In medicine, consensus documents and clinical practice guidelines are important for guiding strategies of prevention, diagnosis, and treatment of different diseases. In this line, the Spanish Society of Cardiology (*Sociedad Española de Cardiología* [SEC]), Spanish Society of Internal Medicine (*Sociedad Española de Medicina Interna* [SEMI]), Spanish Society of Family and Community Medicine (*Sociedad Española de Medicina Familiar y Comunitaria* [semFYC]), Spanish Society of General and Family Practitioners (*Sociedad Española de Médicos Generales y de Familia* [SEMG]), and Spanish Society of Primary Care Physicians (*Sociedad Española de Médicos de Atención Primaria* [SEMERGEN]) have collaborated on the drafting of a consensus document based on analysis of the available published evidence and expert clinical opinion. The aim of this document is to define the impact of polypill use on treatment adherence in patients receiving secondary CV prevention.

This publication presents the main recommendations taken from the consensus document⁷ together with the final percentage of agreement obtained in the last vote (A) and categorization of the recommendations by level of evidence (LE) and grade of recommendation (GR), according to a modified version of the Scottish Intercollegiate Guidelines Network (SIGN) system.⁸

METHODS

The consensus document was developed using a process based on the RAND/UCLA method. A scientific committee of 5 experts was formed and a team including 10 experts was in charge of drafting the recommendations; these professionals agreed on the subject index of the document. A systematic literature search was then conducted according to a previously established protocol focused on updating a comprehensive systematic review on the polypill for secondary CVD prevention performed in 2014. The literature search was carried out in MEDLINE (PubMed), with priority given to clinical practice guidelines, systematic reviews,

* Corresponding author: Hospital Clínico Universitario de Santiago de Compostela, Travesía da Choupana s/n, 15706 Santiago de Compostela, A Coruña, Spain.

E-mail address: Jose.Ramon.Gonzalez.Juanatey@sergas.es (J.R. González-Juanatey).

and consensus documents. In total, 221 documents were retrieved in the first search, resulting in 188 publications after elimination of duplicates. According to the title and abstract, 48 publications were finally selected for the review. The team drafting the recommendations formulated their proposals based on the statements found in the systematic review and their clinical experience. Then, using a modified Delphi process, the statements and proposals made by the team underwent a round of validation by the entire panel of experts. All recommendations with at least 85% of votes in favor were accepted. Because of the high level of consensus in the first round, there was no need for a second validation round. After the Delphi round, uncertain statements and recommendations (< 85% agreement) were discussed in a consensus meeting attended by all the expert participants.

KEY RECOMMENDATIONS

Expected Benefits in Candidate Patients for the Polypill

Several clinical trials have shown that treatment with aspirin, ramipril, and statins reduces CV complication rates, particularly in patients receiving secondary prophylaxis for ischemic heart disease. Furthermore, the reductions in these events are estimated to be greater with combined administration of the 3 drugs than with administration of each drug separately.⁹ Nonetheless, the clinical and prognostic impact of administering these drugs in a single capsule has received little attention in the literature. Although the effects of this therapy on decreasing CV complications has not been well documented, some studies have shown benefits in lowering blood pressure and even in reducing overall mortality^{10,11} (LE 1++).

There are no studies investigating the associated cost or cost-effectiveness of the polypill in Spain, but 1 recent study has reported a model-based cost-effectiveness analysis in the United Kingdom. The model estimated that for each 10% increase in adherence, CV complications would decrease by 6.7%, assuming that adherence to the polypill regimen would be 20% higher than adherence to the regimen of each component separately. The study concluded that the polypill was cost-effective compared with multiple monotherapy in 81.5% of the models at a willingness-to-pay threshold of £20 000 per quality-adjusted life year.¹²

In summary, therapy simplification results in better adherence and better control of CV risk factors, both in primary and secondary prevention¹³ (LE 1+), and could have a significant impact on the rate of CV-related complications¹⁴ (A 100%, LE/GR 4/D).

With regard to patients who properly adhere to their multiple monotherapy regimen, simplification with a fixed-dose combination could favor long-term adherence, especially in those receiving numerous medications and those who have difficulty understanding their disease and its treatment.

Clinical Situations in Secondary Cardiovascular Prevention in Candidate Patients for Polypill Administration

In the setting of secondary CVD prevention and considering that therapy with the 3 drugs comprising the polypill is indicated in patients with a coronary or ischemic cerebrovascular complication and those with symptomatic peripheral arterial disease, the criteria that could determine a preferable indication for fixed-dose combination therapy are shown in Table 1. In addition, initiation of therapy with the polypill could be evaluated during hospitalization if clinicians anticipate that a patient may have difficulties with adherence or access to treatment.

The fixed-dose combination would not be indicated when this strategy is not expected to accomplish the therapeutic objectives stated in the clinical practice guidelines or at least an acceptable approximation to these objectives. Nor would it be indicated in patients who experience adverse effects related to any of the 3 components of the polypill (A 83%).

The main factors that would prompt a switch from multiple monotherapy to the polypill are patient nonadherence, difficult access to the treatments, use of several other drugs, and possible economic advantages. In all patients, it is essential to ensure that the therapeutic goals for low-density lipoprotein cholesterol and blood pressure are reached. If this is not the case, the attending physician could consider adding extra doses of other drugs to attain these goals. In this situation it may be necessary to return to individual dosing of the components to verify that the reason goals were not attained was not a lack of adherence to the polypill, because if that were the case, the problem might be exacerbated by increasing the number of drugs received.

The recommendations for administration of the polypill in patients receiving individual monotherapies that include an angiotensin II receptor blocker or a statin other than atorvastatin are shown in Table 2. An individualized therapy approach should always be considered before a change in therapy, taking into account the low-density lipoprotein goals according to individual CV risk¹⁷ (A 100%, LE/GR 4/D).

Other Clinical Situations in Which Polypill Use May Be Beneficial

The presence of subclinical CVD places patients at high or very high CV risk; hence, most will be candidates for a pharmacological intervention to control the risk and provide protection from organic disease. Despite their high CV risk, the asymptomatic nature of the patients' condition and lack of a previous CV event may lead to poor adherence to the therapy prescribed. Therefore, many could benefit from a therapeutic strategy that would facilitate adherence, such as a fixed-dose combination therapy, whose composition includes the drug groups with proven benefit in subclinical CVD. The recommendations for polypill use in patients with subclinical CVD are summarized in Table 3.

As to patients in primary prevention for high or very high CV risk but without subclinical CVD, there is some evidence on the efficacy and safety of fixed-dose therapy in this population.¹⁸ Nonetheless, the lack of robust evidence supporting the use of ASA in primary CV prevention is an obstacle to reaching a consensus on whether the polypill should be recommended in these patients.

Limitations, Precautions, and Contraindications of the Polypill

In the framework of any chronic treatment, it is important to know the potential drawbacks and risks associated with administration of fixed doses of various drugs. In the case of the polypill, the main problem would be failure to reach the required or optimal goals for controlling CV risk.

Table 1

Criteria that Could Lead to a Preferential Indication for the Polypill in Secondary Prevention of Cardiovascular Disease

- Patients with a history of poor adherence to drug therapy or who have risk factors predicting poor adherence
- Patients who are not well controlled with equivalent doses and have problems of adherence
- Patients who are well controlled with the individual drugs
- Patients with comorbidities and receiving several drugs

Table 2

Recommendations for Polypill Administration in Patients Treated With an Individualized Regimen Including an Angiotensin II Receptor Blocker or Statin Other Than Atorvastatin

Recommendations	Agreement	LE/GR
The ARB can be replaced by an ACE inhibitor, except in patients who have experienced a previous adverse event with ACE inhibitors, such as cough or angioneurotic edema ¹⁵	93%	1++/A
A switch to the polypill can be used in patients who take statins other than atorvastatin, provided that the low-density lipoprotein cholesterol-lowering capacity is maintained at equivalent levels (moderate cholesterol-lowering intensity) ¹⁵	93%	4/D
For patients who require a more potent effect than that provided by atorvastatin 20 mg, a switch to the polypill is not advisable because the loss of lipid-lowering capacity may be accompanied by decreased treatment benefits and increased risk ¹⁶	100%	2+/D

ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme; GR, grade of recommendation; LE, level of evidence.

Table 3

Recommendations on the Benefits of the Polypill for Patients at High or Very High Cardiovascular Risk With Subclinical Cardiovascular Disease

Recommendations	Agreement
<i>Current evidence suffices to consider polypill use in the following subgroups of patients with subclinical cardiovascular disease, provided they do not have a high risk of bleeding:</i>	100%
1. Hypertensive patients at high cardiovascular risk, defined by the following: left ventricular hypertrophy, microalbuminuria/proteinuria, renal failure, increased pulse wave velocity, increased carotid intima-media thickness, presence of atheromatous plaques, or an abnormal ankle-brachial index	
2. Patients with diabetes, hypertension, and microalbuminuria/proteinuria, regardless of the presence or absence of the remaining markers of subclinical disease. Can also be considered in the absence of hypertension	

Comparative data are lacking on the rates of adverse effects associated with the polypill vs separate administration of the 3 drugs. However, in studies performed with other fixed-dose treatments, the use of these presentations has been associated with a slight rise in the rate of mild adverse effects compared with individual administration of the components, which has been attributed to better adherence¹¹ (LE 1++). Therefore, the precautions when using the polypill for CV prevention are derived from those associated with aspirin, ramipril, and atorvastatin; an increase in the risk of adverse effects due to drug interactions is not expected.

The most common reason for unintentional lack of treatment adherence is forgetting to take the medication, and the approved dosing regimen of the polypill is the same as for the 3 components taken separately. A single polypill capsule should be taken daily, preferably following a meal to minimize possible gastrointestinal adverse effects from aspirin therapy. When patients forget to take the polypill, they should take their normal dose at the scheduled time the next day.

Even though a patient may be following an appropriate drug regimen for CV risk prevention, the persistent residual risk may be similar to or greater than the risk eliminated by prevention. Hence, the drug therapy used (in this case the polypill) should be associated with lifestyle habits and behavior that contribute to lowering this residual risk.¹⁹ Patients treated pharmacologically for primary or secondary CV prevention with or without the polypill should have heart-healthy lifestyle habits that include stopping smoking, an appropriate diet, physical activity, avoiding obesity, and controlling the classic CV risk factors (eg, diabetes mellitus, hypertension, dyslipidemia). Lastly, patients in treatment with the polypill should understand that simplification of the treatment does not make it any less important.

ACKNOWLEDGEMENTS

The authors wish to express their appreciation for the work of the expert team that participated in developing the consensus document: Gonzalo Barón-Esquívias (SEC), Enrique Galve (SEC), Rosa María Lidón (SEC), Francisco Xavier García-Moll (SEC), Pedro Luis Sánchez (SEC), Carmen Suárez (SEMI), Jesús Millán (SEMI), Vicente Pallarés (SEMERGEN), José Juan Alemán (semFYC) and

Isabel Egocheaga (SEMG), and extend their thanks to Ferrer for valuable support and GOC Networking for technical and methodological assistance.

FUNDING

Ferrer funded the logistics required to develop the document, but did not participate in any of the related debates or decisions.

CONFLICTS OF INTEREST

None declared.

REFERENCES

- López-Sendón J, González-Juanatey JR, Pinto F, Cuenca Castillo J, Badimón L, Dalmau R, et al. Indicadores de calidad en cardiología. Principales indicadores para medir la calidad de los resultados (indicadores de resultados) y parámetros de calidad relacionados con mejores resultados en la práctica clínica (indicadores de práctica asistencial). INCARDIO (Indicadores de Calidad en Unidades Asistenciales del Área del Corazón): Declaración de posicionamiento de consenso de SEC/SECTCV. Rev Esp Cardiol. 2015;68:976–95.e10.
- Fuster V. Un problema alarmante en prevención secundaria, bajo cumplimiento (estilo de vida) y baja adherencia (farmacológica). Rev Esp Cardiol. 2012;65 Supl 2:10–6.
- Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M, et al. Full coverage for preventive medications after myocardial infarction. N Engl J Med. 2011;365:2088–97.
- Phan K, Gomez YH, Elbaz L, Daskalopoulou SS. Statin treatment non-adherence and discontinuation: clinical implications and potential solutions. Curr Pharm Des. 2014;20:6314–24.
- Bryant L, Martini N, Chan J, Chang L, Marmoush A, Robinson B, et al. Could the polypill improve adherence? The patient perspective. J Prim Health Care. 2013;5:28–35.
- Sanz G, Castellano JM, Fuster V. Policomprimido: ¿quimera o realidad? Rev Esp Cardiol. 2014;67:689–92.
- González-Juanatey JR, Mostaza JM, Lobos JM, Abarca B, Llisterri JL. Nuevo enfoque terapéutico para la prevención secundaria del riesgo cardiovascular. Documento de consenso del uso clínico de la Polypill [accessed 2016 Jan 8]. Available at: http://www.revespcardiolo.org/contenidos/static/docs/Consenso%20Polypill_v4_2.pdf
- Scottish Intercollegiate Guidelines Network. SIGN 50: A Guideline Developers' Handbook. Edinburgh: SIGN; 2001 [accessed 2013 May 3]. Available at: <http://www.sign.ac.uk/guidelines/fulltext/50/index.html>

9. Fuster V, Sanz G. Compuestos de dosis fija en la prevención secundaria de la cardiopatía isquémica. *Rev Esp Cardiol.* 2011;64 Supl 2:3–9.
10. Thom S, Poulter N, Field J, Patel A, Prabhakaran D, Stanton A, et al. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. *JAMA.* 2013;310:918–29.
11. De Cates AN, Farr MR, Wright N, Jarvis MC, Rees K, Ebrahim S, et al. Fixed-dose combination therapy for the prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2014;CD009868.
12. Becerra V, Gracia A, Desai K, Abogunrin S, Brand S, Chapman R, et al. Cost-effectiveness and public health benefit of secondary cardiovascular disease prevention from improved adherence using a polypill in the UK. *BMJ open.* 2015;5:e007111.
13. Castellano JM, Sanz G, Fernandez Ortiz A, Garrido E, Bansilal S, Fuster V. A polypill strategy to improve global secondary cardiovascular prevention: from concept to reality. *J Am Coll Cardiol.* 2014;64:613–21.
14. Castellano JM, Sanz G, Penalvo JL, Bansilal S, Fernandez-Ortiz A, Alvarez L, et al. A polypill strategy to improve adherence: results from the FOCUS project. *J Am Coll Cardiol.* 2014;64:2071–82.
15. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens.* 2009;27:2121–58.
16. Colivicchi F, Tubaro M, Santini M. Clinical implications of switching from intensive to moderate statin therapy after acute coronary syndromes. *Int J Cardiol.* 2011;152:56–60.
17. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129(25 Suppl 2):S1–45.
18. Yusuf S, Attaran A, Bosch J, Joseph P, Lonn E, McCreedy T, et al.; Working Group on the Summit on Combination Therapy for CVD. Combination pharmacotherapy to prevent cardiovascular disease: present status and challenges. *Eur Heart J.* 2014;35:353–64.
19. Castellano JM, Narula J, Castillo J, Fuster V. Promoción de la salud cardiovascular global: estrategias, retos y oportunidades. *Rev Esp Cardiol.* 2014;67:724–30.