A Polypill strategy at the Heart of cardiovascular secondary prevention

Borja Ibañez*[1,2,3], MD PhD; José M Castellano[1,4,5], MD PhD; Valentin Fuster[1,6], MD PhD.

Authors Affiliation:

[1]Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain;

[2]Cardiology Department, IIS-Fundación Jiménez Díaz Hospital, Madrid, Spain;

[3]CIBER de enfermedades CardioVasculares (CIBERCV), Spain;

[4]Centro Integral de Enfermedades Cardiovasculares (CIEC), Hospital Universitario Montepríncipe, HM Hospitales, Madrid, Spain

[5]Facultad de Medicina, Universidad CEU San Pablo, Madrid, Spain

[6]Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, USA.

Key words: Prevention; Polypill; adherence; myocardial infarction; stroke; guidelines; atherosclerosis.

***Address for correspondence:**

Borja Ibáñez, MD PhD

Director Clinical Research Department, Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Melchor Fernández Almagro, 3, 28029, Madrid, Spain & IIS-Fundación Jiménez Díaz, Madrid, Spain. Email: bibanez@cnic.es

Over recent decades, cardiovascular disease (CVD) has overtaken infectious diseases as the leading cause of death worldwide.[1] This shift is partly due to the great advances in the treatment of infectious diseases and the success of associated public health campaigns. General public awareness of the importance both of preventing high-risk exposure and of early therapy initiation and adherence has helped reduce the burden of communicable (infectious) diseases. This contrasts sharply with the story of non-communicable diseases such as CVD. The incidence of atherosclerosis (the single largest underlying cause of CVD) has increased exponentially due to the immense lifestyle changes witnessed first in developed countries but lately also in low- and middle-income countries. This rapid worldwide change in lifestyle has resulted in dramatic increases of obesity, sedentarism, dyslipidemia, and hypertension, all of which are risk factors for atherosclerosis;

The control of modifiable cardiovascular risk factors, such as lipid levels, blood pressure, etc., has a clear impact in reducing the likelihood of experiencing a cardiovascular event, and this holds true for both primary and secondary prevention. The leading cardiovascular scientific societies dedicate major efforts to providing guidelines to enable clinicians to define specific targets for each of these modifiable factors based on a patient's risk profile. The most recent European Society of Cardiology (ESC) "Guidelines on cardiovascular disease prevention in clinical practice", released in 2016, established low density lipoprotein (LDL)-cholesterol targets of 70, 100, and 115 mg/dL for individuals at very high, high, and low-to-moderate risk, respectively, and a blood pressure target of <140/90 mmHg (140/85 mmHg for most patients with diabetes).[2] The identification of risk factors allows gross prediction of future cardiovascular events such as myocardial infarction (MI), stroke, etc.

Patients experiencing an acute cardiovascular event today have a high likelihood of surviving the episode thanks to the great therapeutic advances in MI and other acute conditions. However, these patients remain at high risk of subsequent events, with long-term consequences for the affected individuals (disability, absenteeism, etc.) and for health care budgets. Clinical research over recent decades has identified several pharmacological routes to effectively reducing the incidence of adverse events in survivors of MI and other acute conditions. These therapeutic options all receive clinical practice guideline recommendations for specific conditions.[3, 4] Task forces commissioned to prepare these documents review available data about the efficacy of specific therapies. In devising these recommendations, the greatest weight is given to evidence from adequately powered randomized clinical trials. However, it is important to bear in mind that patients enrolled in clinical trials are monitored closely, and medication adherence is therefore usually high. In real life treatment adherence is significantly lower than in controlled trials, with the result that the real-life efficacy of prescription drugs is lower than anticipated. Data from European cohort studies found that up to 9% of all CVD events can be attributed to poor adherence to cardiovascular medications.[5] In a recent analysis of ≈4000 post-MI patients, patients fully adhering to medication (taking prescribed drugs >80% of days) had a significantly lower incidence of major adverse cardiovascular events (MACE) than those with partial adherence (40-80% of days covered) or non-adherence (<40%) (MACE incidence 19%, 25%, and 26%, respectively).[6] In addition, full treatment adherence results in lower per-patient annual direct medical costs for MI hospitalization than partial or non-adherence.[6] One major reason for non-adherence to secondary prevention medication is the complexity of treatment, which usually involves a high number of daily prescribed pills.[7] This problem is by no means specific to CVD, but affects many other conditions requiring treatment combinations. The introduction of a polypill strategy for patients with infectious diseases (tuberculosis, HIV, etc.) has successfully facilitated access and adherence to medication, and has even reduced associated distribution costs.[8] These polypills have become the mainstay therapy for most patients with these infectious diseases. Atherosclerosis seems a perfect scenario for the adoption of a polypill strategy, since clinical practice guidelines recommend a high number of medications after an acute event.[3, 4] Unexpectedly, although one secondary prevention cardiovascular polypill containing aspirin, ramipril, and atorvastatin received approval from the European Medicines Agency (EMA) in 2014,[9] this strategy has not been universally adopted.

In the present issue of the journal, Selak and colleagues[10] present an individual participant data meta-analysis of three randomized clinical trials comparing a polypill strategy (containing aspirin, a statin, and an

antihypertensive drug) with standard care. The main goal of the analysis was to determine the proportion of patients in the polypill and usual care arms meeting 2016 ESC prevention guideline[2] targets for LDL-cholesterol, blood pressure, and antiplatelet use. The analysis included 3140 patients with a prior CVD event (secondary prevention) or who were at high risk of their first event (primary prevention). The trials included in the meta-analysis were IMPACT (n≈500 patients), Kanyini-GAP (n≈600), and UMPIRE (n≈2,000). The three trials were conducted between 2010 and 2013 as part of the pre-established SPACE (Single Pill to Avert Cardiovascular Events) collaboration. The three trials thus followed the same protocol, with only minor regional adaptations.[11] The SPACE consortium already published the results of an individual participant data meta-analysis of these trials,[12] showing that the polypill strategy significantly improved medication adherence, resulting in a significant improvement in systolic blood pressure and LDL-cholesterol levels compared with usual care.[12] In the present study, Selak and colleagues used the same database to determine if these improvements resulted in a higher proportion of patients meeting the targets set by the ESC prevention guidelines.[2] The main finding of the present study is that a higher proportion of patients in the polypill arm achieved the recommended targets for LDL-cholesterol (39% in polypill vs 34% in usual care) and blood pressure (62% vs 58%). Adherence to antiplatelet therapy (only applicable to secondary prevention patients) did not differ (96% in both arms). The proportion of patients meeting the three targets simultaneously was significantly higher in patients included in the polypill arm than in those in the usual care arm (24% vs. 19%). Despite being a not pre-specified analysis, these results are very important and provide significant incremental information to their previous meta-analysis.[12] One limitation of this analysis is that it only presents data collected in the SPACE collaboration trials, which were conducted 5-8 years ago. Relevant data from more recent trials, like the FOCUS (Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention) trial[13] were not included. In the European Union FP7-funded FOCUS trial, ≈700 post-MI patients were randomized to a polypill strategy (aspirin, statin and ramipril) or to usual care. Adherence to medication was significantly higher in the polypill strategy group (51% vs 41% in usual care group).[13] After completion of the FOCUS trial, the cardiovascular "*Fuster polypill*"—containing aspirin, ramipril, and a statin—received approval for clinical use in 2014 and is currently available in more than 30 countries.[9]

As the Salek study confirms, the evidence supporting the benefits of a cardiovascular polypill strategy in high risk patients is compelling. Given that this strategy results in higher treatment adherence and better control of modifiable risk factors, the 2016 ESC cardiovascular prevention guidelines included for the first time a recommendation for its use.[2] A year later, the 2017 ESC guidelines for the treatment of patients with ST-segment elevation myocardial infarction[4] included the same recommendation, in line with the prevention guidelines. In these two major ESC guideline documents, the class of recommendation for the cardiovascular polypill is set at IIb, with a level of evidence B. Given the consistent benefits across trials, one might question why the class of recommendation for this strategy is not stronger. The main reason is the lack of direct data showing that the increased adherence and better control of risk factors associated with the use of the cardiovascular polypill result in significant reductions in hard endpoints. To date no trial has had the power to test this hypothesis. To address this need, the European commission (H2020)-funded SECURE (Secondary Prevention of Cardiovascular Disease in the Elderly) trial is being conducted under the coordination of the Spanish National Center for Cardiovascular Research (CNIC) in Spain (ClinicalTrials.gov Identifier: NCT02596126). The ongoing SECURE trial will randomize 3200 post-MI patients in 7 European countries (Spain, Italy, Czech Republic, Germany, France, Poland, and Hungary) to receive the "*Fuster Polypill*" (aspirin, ramipril, and atorvastatin) or to usual care (the 3 medications separately). This study is powered to identify differences in MACE (cardiovascular death, nonfatal MI, nonfatal ischemic stroke, and urgent revascularization) over a minimum 2-year follow-up. The bad news is that results of this trial will not be available before 2022.

In summary, there is robust evidence that the use of a cardiovascular polypill strategy results in increased adherence to treatments, to better control of modifiable risk factors, and to a higher proportion of patients meeting ESC guideline targets for LDL-cholesterol and blood pressure. Although there is still no data showing that these benefits translate into a reduction in hard endpoints, adoption of this strategy can now be considered in daily practice.

Disclosures:

Borja Ibanez and Valentin Fuster have no personal conflicts of interest to declare. José María Castellano has received speaker fees and travel support from Ferrer. The CNIC is a nonprofit public institution that receives royalties for the sales of a polypill (Trinomia®) composed of aspirin, ramipril, and atorvastatin, but no CNIC researcher has direct interests or receives any personal benefits.

REFERENCES

1 Castellano JM, Fuster V, Jennings C, et al. Role of the polypill for secondary prevention in ischaemic heart disease. *Eur J Prev Cardiol* 2017;**24**:44-51.
2 Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315-81.
3 Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267-315.
4 Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119-77.
5 Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013;**34**:2940-8.
6 Bansilal S, Castellano JM, Garrido E, et al. Assessing the Impact of Medication Adherence on Long-Term Cardiovascular Outcomes. *J Am Coll Cardiol* 2016;**68**:789-801.
7 Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation* 2009;**119**:3028-35.
8 Panchagnula R, Agrawal S, Ashokraj Y, et al. Fixed dose combinations for tuberculosis: Lessons learned from clinical, formulation and regulatory perspective. *Methods Find Exp Clin Pharmacol* 2004;**26**:703-21.
9 Webster R, Castellano JM, Onuma OK. Putting polypills into practice: challenges and lessons learned. *Lancet* 2017;**389**:1066-74.
10 Selak V, Webster R, Stepien S, et al. Reaching cardiovascular prevention guideline targets with a polypill-based approach: a metaanalysis of randomized clinical trials. *Heart* 2018:00-.
11 Selak V, Elley CR, Crengle S, et al. IMProving Adherence using Combination Therapy (IMPACT): design and protocol of a randomised controlled trial in primary care. *Contemp Clin Trials* 2011;**32**:909-15.
12 Webster R, Patel A, Selak V, et al. Effectiveness of fixed dose combination medication ('polypills') compared with usual care in patients with cardiovascular disease or at high risk: A prospective, individual patient data meta-analysis of 3140 patients in six countries. *Int J Cardiol* 2016;**205**:147-56.
13 Castellano JM, Sanz G, Penalvo JL, et al. A polypill strategy to improve adherence: results from the FOCUS project. *J Am Coll Cardiol* 2014;**64**:2071-82.