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Polypill: an affordable strategy for cardiovascular disease prevention in low–medium-income countries

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Abstract: The simplification of fixed dose medications by using a single 'polypill' is an attractive strategy to improve adherence to medications which has shown benefit to cardiovascular risk factor control and cardiovascular disease prevention or delay in the progression of these diseases. We review the evidence obtained from a series of clinical trials demonstrating an improvement in adherence to the polypill compared to the use of each compound separately, and found similar or better control of the classical cardiovascular risk factors and a similar safety profile. These results suggest that the use of the polypill could have a beneficial impact in cardiovascular morbidity and mortality. Furthermore, the polypill has the potential to improve cost effectiveness and is simple to use. However, before recommending the implementation of the polypill in programs aimed at primary and secondary cardiovascular prevention, we are awaiting the results of several current clinical trials aimed at measuring the impact on the frequency of major cardiovascular outcomes, particularly in low–medium-income countries.

Keywords: cardiovascular disease, compliance, fixed dose combination therapy, hypertension, polycap, polypill

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Introduction

Cardiovascular disease (CVD) is the major cause of mortality and morbidity globally, affecting half of all individuals over their lifetimes.[1,2] Although age-adjusted mortality for CVD is decreasing in developed countries, this figure has risen substantially in developing countries.[3] Nearly 80% of noncommunicable disease (NCD) deaths (29 million) occur in low- and medium-income countries (LMIC), and CVD is the leading cause (17 million deaths, or 48% of NCD deaths).[4] In addition, CVD occurs at a younger age in developing countries. It has been estimated that in LMICs, three times as many disability-adjusted years lost (DALYs) occur than in high-income countries (HICs). Consequently, by 2020, LMICs are expected to account for approximately three quarters of the global mortality, and 80% of the disease burden (as measured by DALYs).[5] Furthermore, hypertension control[6] and the use of medications for secondary prevention are lowest in low-income countries (LICs) and medium-income countries (MICs).[7] The Population Urban and Rural Epidemiology (PURE) study found that in LMICs' medication use rates were as low as 8.8% for antiplatelet medications, 9.7% for angiotensin-converting enzyme inhibitors (ACEIs) and 3.3% for statins among community-based patients with existing CVD, individuals who, in the absence of contraindications, should be receiving those medications. Moreover, in LICs, 80% of patients with a prior CVD event reported taking no cardiovascular preventive medications, compared with 69% in lower MICs, 45.1% in upper MICs and 11% in HICs.[7]

In the South American countries participating in the PURE study (Argentina, Brazil, Chile and Colombia), the proportion of individuals with coronary heart disease (CHD) who received antiplatelet medications (30.1%), beta-blockers (34.2%), angiotensin-converting enzyme inhibitors ACEIs or angiotensin-receptor blockers (36.0%), or statins (18.0%) were as low as that observed in LMICs globally; and even lower amongst stroke patients (antiplatelet 24.3%, ACEIs/angiotensin-receptor blockers 37.6%, statins 9.8%). Furthermore, a substantial proportion of patients did not receive any proven therapy (CHD 31%, stroke 54%).[8] Clearly, strategies to identify and overcome barriers and enhance CVD prevention worldwide are essential, particularly in LMICs.

In 2002, Yusuf[9] proposed a four-drug combination of aspirin (ASA), beta blocker (BB), statin and ACEI to reduce cardiovascular events in secondary prevention and estimated that its use would result in a cumulative risk reduction of 75% in CVD events. In 2003,[10] Wald and Law estimated that a polypill could potentially reduce CHD events by 88% and stroke by 80% and suggested that it should be prescribed to all individuals with a CVD event (secondary prevention), and to anyone over 55 years (primary prevention) without the need to measure risk factors, as advancing age is the principal risk factor for a CVD event.

In recent years, a considerable amount of research has addressed the effects of combining agents controlling different cardiovascular risk factors in a single tablet. In the present paper, we will review the evidence of recent clinical research that suggests that the use of the polypill could be a useful strategy in the fight against the epidemic of CVD and particularly in LMICs, where resources are limited and the availability and affordability of these four drugs with demonstrated beneficial cardiovascular effects are so low[7,8,11]

Primary prevention for cardiovascular disease

Primary prevention for CVD is defined as individual or community actions targeted to a population with risk factors, but without the presence of the disease.[12] The individual approach involves screening vulnerable patients. This strategy has the advantage of early prevention, optimization and adaptation of the intervention, depending on the patient, but has high costs of detection, and the prediction of the risk in primary prevention could be inaccurate and not reflect the real risk in the long term.[13] Because of this inaccuracy in the assessment of long-term risk, the treatment of at-risk patients has been questioned. Moreover, it is known that the use of risk scores based on risk factor thresholds can ignore a high proportion of cardiovascular events.[13]

Primary prevention should include various strategies such as health policies, environmental changes and the use of safe and already approved medicines. In this context, a polypill would be given to patients over a certain age who are not necessarily indicated for all the individual components of the polypill. This strategy could either target whole populations or those in at-risk populations without CVD.[14] Moreover, the polypill could improve the low adherence to prescribed treatments, which is one of the major barriers to prevention of CVD in South American countries.[8,15] The impact of the polypill in CVD primary prevention across five studies that included 1142 high-risk individuals was reviewed by Chrysant[16] who concluded that the polypill was useful for the primary prevention of CVD by decreasing blood pressure and low-density lipoprotein cholesterol (LDL-C) concentration. Recently, Huffman *et al.*[17] extensively reviewed current evidence on the efficacy and safety of polypills in CVDs based on results from 13 polypill trials (9059 participants) across 32 countries. This included all of the secondary prevention clinical trials, high-risk primary prevention based on formal risk assessment, and primary prevention based on single risk factor measurement. The authors concluded that all polypills used improve adherence, are well tolerated, and reduce risk factor levels. Both reviews support the recommendation of the use of a polypill for the prevention of CVD in individuals without antecedents of CVD and intermediate risk. The results of the recent HOPE-3 study[18] provide additional support for this proposal. This international clinical trial included 12,705 people aged over 55 (men) or 60 (women) without CVD, and with intermediate cardiovascular risk and with one additional cardiovascular risk factor, which was abdominal obesity in 87% of the sample. Inclusion criteria for participation was blood pressure less than 160/90 mmHg and LDL-C $<$ 130 mg/dl, and patients were randomized in a double-blind design to receive rosuvastatin 10 mg/day *versus* placebo[19] or candesartan 16 mg and hydrochlorothiazide 12.5

mg/day *versus* placebo[20] or a combination of candesartan 16 mg, hydrochlorothiazide 12.5 mg and rosuvastatin 10 mg/day *versus* placebo.[21] Individuals in the highest tertile of systolic blood pressure (>143 mmHg, median 154 mmHg) that received the three medications achieved significant reductions in relative risk (45%) and absolute risk (0.5%) of acute myocardial infarction, and of stroke (relative reduction; 44%, absolute risk reduction; 0.8%). This study demonstrated for the first time the effectiveness of the combined administration of a half dose of two antihypertensive agents (angiotensin II receptor blocker and diuretic) and statin in the primary prevention of CVD in individuals with intermediate risk and without CVD.

Secondary prevention for cardiovascular disease

The main goal of secondary prevention is to decrease morbi–mortality through programs that use effective strategies. A high proportion[22] of CVD deaths occurs in people who already had an event and in these individuals, mortality can be reduced with appropriate pharmacological and lifestyle management.[23] The World Health Organization (WHO) recommends[24] that secondary CV-prevention patients (individuals who have had a heart attack or ischemic stroke) should, in addition to lifestyle changes, take an antiplatelet agent, statin, and blood-pressure-lowering drugs for the long term, to reduce the risk of a recurrent nonfatal or fatal CVD events, an approach that is also recommended by several international guidelines and studies.[25–28]

In the PURE study,[29] we found low levels of adoption of lifestyle changes in individuals with coronary heart disease and stroke, particularly in poorer countries, indicating that great efforts must be made to make changes in lifestyle an effective therapeutic strategy in secondary cardiovascular prevention. Moreover, as discussed before, the proportions of individuals with CHD who received pharmacological treatment was very low,[7] a situation related to the poor availability and affordability of CVD medicines[11] in Latin America and other LMICs.[8] Moreover, it is estimated that compliance in secondary cardiovascular prevention patients is low and tends to decrease over time.[30,31] After 6 months of treatment, on average, 50% or more of the patients quit the pharmacological treatment and the lifestyle modifications.[31] Low compliance with treatment is a barrier that has a great impact on patient's health, carries a greater incidence of mortality, and increases healthcare cost *via* increased hospitalization rates.[32] It is now known that adequate compliance and CVD control are directly associated.[33] Other barriers that explain the low levels of cardiovascular secondary medication use in Latin America, particularly in rural areas, include limited access to healthcare system, lack of regular healthcare provider and difficulty in transportation for medical visits.[15]

Fixed-dose combination: cost effectiveness

The WHO 2013 Global Action Plan for the Prevention and Control of Non-Communicable Diseases (NCDs) includes nine global targets.[34] One of these goals is that at least 50% of people at high risk of CVD (including those who have had a prior event) receive multidrug treatment to prevent heart attacks and strokes. Another of the nine targets is an 80% availability of the affordable basic technologies and essential medicines required to treat major NCDs.[35] Polypharmacy is frequent in medical care[36] and fixed-dose combination therapy is an intervention that has the potential to substantially enhance access to multidrug therapy by making recommended medicines more accessible.[22,37] Gaziano and colleagues[38] performed a cost-effectiveness study assessing two combinations of medications. One regimen for primary prevention included aspirin, a calcium channel blocker, an ACEI and a statin. The regimen for secondary prevention included the same combination of drugs but substituted a beta blocker for the calcium channel blocker. The incremental cost-effectiveness ratio for the secondary regimen was between $306 and $388 per quality-adjusted life-year, indicating this as a cost-effective intervention for patients with CVD in all developing regions, even in LMICs. Moreover, fixed-dose combinations decrease healthcare costs by decreasing the number of hospitalizations and disabilities due to CVDs.[39] For example, in the United Kingdom, it was calculated that the implementation of fixed-dose therapy programs for primary prevention in patients older than 50 years could result in a net gained saving of £2,000 per year of life with the prevention of a first myocardial infarction or stroke, since the polypill provided cost was £1 per person per day, a cost-effective solution.[22]

Other studies that have assessed the cost effectiveness of polypill with different screening strategies and cost and affordability estimations support

its cost effectiveness,[37–39] and suggest that the polypill is one of the most cost-effective interventions in CVD prevention. Moreover, the increase in adherence also contributes to the cost effectiveness of the polypill intervention. The indirect and direct costs of nonadherence to treatments for chronic illnesses in the US have been estimated as between $100 billion and $289 billion annually. In the European Union, poor adherence to antihypertensive and cardiovascular medication costs €1.25 billion annually.[39]

The TIPS 3: a polypill study in low–medium-income countries

Presently, several clinical studies are underway, with the aim of evaluating the safety and efficacy of the polypill, including TIPS 3, HOPE-4, OMS, PILL, UMPIRE, SECURE, amongst others.[17]

The TIPS 3[40] is a 2 × 2 clinical trial in CVD primary prevention running currently, aimed at determining the effects of a daily polycap composed of ramipril 5 mg, hydrochlorothiazide 12.5 mg, simvastatin 40 mg and atenolol 50 mg. Eligible persons entered a single-blind run-in phase, during which they received both active treatments (polycap and aspirin) for 4 weeks. Participants adhering to the regimen and who did not have an unacceptable level of adverse events were randomly assigned to polycap or placebo and low-dose aspirin (100mg) or placebo and vitamin D or placebo. This 5-year study has recruited women of aged 60 or older and men aged 55 or older without known heart disease or prior stroke and without a clear indication for or contraindication to any of the study medications. The study has achieved the goal of recruiting 5000 study participants from eight LMICs (Bangladesh, Colombia, India, Indonesia, Malaysia, Philippines, Tanzania, Tunisia) and one HIC (Canada). This study aims to increase medical adherence of patients, decrease cost, and provide evidence that a polypill can reduce CVD morbidity and mortality in people with low cardiovascular risk in LMICs. The results are anticipated in the second half of 2019.

Various polypills of differing compositions have been launched and are found in the pharmacies of more than 30 countries. It is expected that the commercialization of the polypill would spread worldwide, especially in LMICs who are seeking a large impact on health and economics.[17]

Limitations of the polypill strategy

The polypill is an effective, easy and attractive antihypertensive treatment, but several issues may limit its implementation worldwide. For example, the strategy cannot be applied to all patients because it is impossible to individualize the doses of its components, especially in individuals who may present with contraindications or adverse effects for one or more ingredients.[14] For example, in HOPE-3,[20] muscle weakness and cramps were more common, making statins a contraindication for those patients (although in HOPE-3, statins were given separately) and potentially reducing compliance amongst patients experiencing these adverse effects. This could be resolved if a variety of versions of the polypill were sold with differing components and proportions of its components.

Another barrier to the free implementation of the polypill are the patents for its components. A study in Canada and the United States assessed the availability of cardiovascular medication with free patents and found that only 40% of cardiovascular medications were totally patent free,[41] which could be a significant barrier for the worldwide marketing and distribution of the polypill. A potential solution to this issue is that the pharmaceutical companies who own the original patents bring the polypill to the market at an affordable price, or generic companies and government research agencies incentivize successful pricing models allowing its easy obtainment and implementation for adequate treatment.[42]

Conclusion

The overall results for a better practice of medicine in relation to CVDs require effective strategies and proposals by the scientific community for widespread implementation. The concept of the polypill and its implementation has the potential to help improve the control of the global CVD epidemic. However, it may be necessary to produce different versions of the polypill which vary in their components, and concentrations of these components, to address the implicit low flexibility of the polypill with respect to dose modification of its individual components, which may expose patients to unnecessary therapy and adverse effects.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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