ORIGINAL ARTICLE

# POLYPILL AND CARDIOVASCULAR PREVENTION A REVIEW

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## SUMMARY:

The majority of people at high risk for cardiovascular disease around the world do not receive any of the optimal preventive medications. Prevention has a physical implication and an economic consequence that transforms it into the pillar of the search for health. The objective of this review was to determine whether fixed-dose combinations of generic drugs (“ polypills “) have been shown to be useful in adherence to treatments, and whether they have contributed to reducing the risks of disease. To do this, we have reviewed the main global studies and trials carried out to date.

## INTRODUCTION

### GENERAL CONSIDERATIONS

Health is a fundamental human right that entails access to necessary medications.

This is basic in any branch of Medicine, but it is especially important in cardiovascular health, since undesirable events in this subgroup are the greatest cause of morbidity and mortality worldwide. Accessibility to medicines is hampered for different reasons.

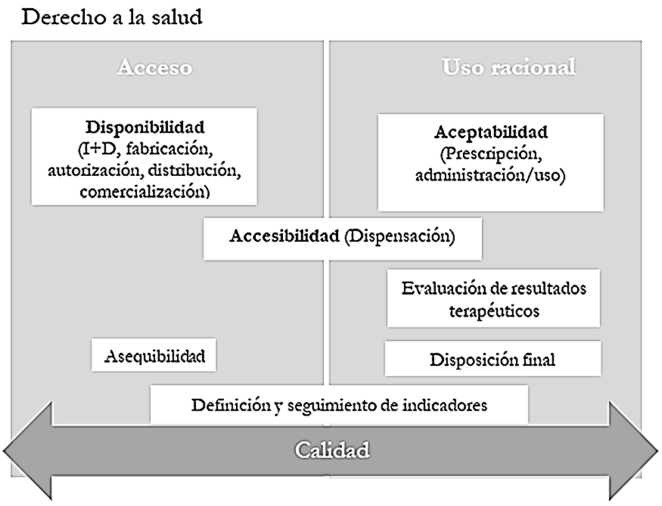
The determinants of access to medicines can be classified into three large groups. On the one hand, there are barriers to access to medication established by the different forms of organization and stratification of each society. On the other hand, access to medicines is a direct function of the protection schemes of health systems. Finally, there are barriers to access that stem from the very economic dynamics of the drug market. The problem of access to medicines is spreading and getting worse all over the world.

That, and other factors, conspire so that the treatments (especially those of long duration) are discontinued, tending to the reappearance of the disease that should be under control.

One consideration that favors the population-based approach is the recognition that many people who have conventional algorithms would classify a cardiovascular event as low or intermediate risk.

There are additional challenges with a risk-based approach in resource-limited settings. It is not clear whether traditional prediction algorithms are applicable to people with low socioeconomic status. Additionally, a risk-based strategy can be difficult to implement due to the need for frequent testing and follow-up visits and complex medication regimens. The combination of drugs in fixed doses offers proven benefits for the prevention of cardiovascular diseases.

In population strategies for the prevention of cardiovascu-



lar diseases, this combination offers potential advantages over conventional pharmacotherapy. First, the simplicity of using a daily pill may improve adherence to therapy. Second, the removal of requirements for dose adjustment may be useful in settings where frequent follow-up visits are impractical.

Third, for blood pressure control, combining multiple low-dose drugs rather than one or two higher-dose drugs may improve the safety profile, since side effects are often dose-dependent.

## CARDIOVASCULAR RISK FACTORS

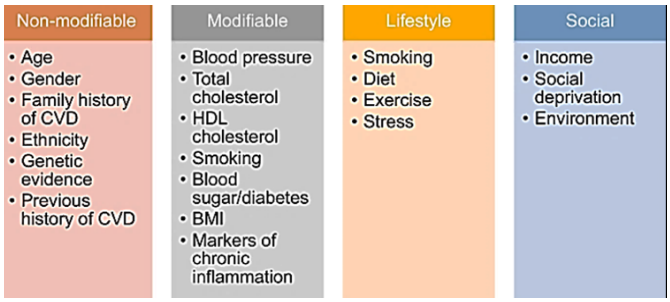
A cardiovascular risk factor (CVRF) is a biological characteristic or a habit or lifestyle that increases the probability of suffering or dying from cardiovascular disease (CVD) in those individuals who present it. [1, 2]

Precisely, since it is a probability, the absence of risk factors does not exclude the possibility of developing a CVD in the future, and their presence does not necessarily imply the appearance of the morbid state.

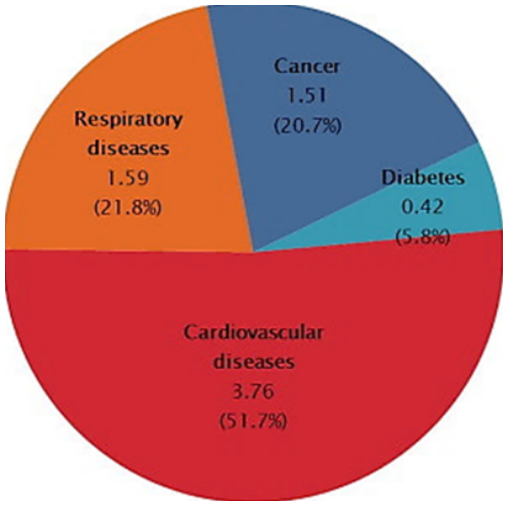
The main risk factors can be non-modifiable (age, sex, genetic factors/family history) or modifiable , the latter being precisely those of greatest interest, since it is necessary to act preventively on them: high blood pressure (HBP), smoking, hypercholesterolemia, diabetes mellitus (DM) and overweight/obesity (particularly abdominal or visceral obesity), frequently associated with physical inactivity.

These are the so-called major and independent risk factors, and they are the ones that have a stronger association with CVD, being very frequent in the population. Other CVRFs that are associated with an increased risk of CVD are low high-density lipoprotein cholesterol ( HDL -C ) and high triglycerides, as an expression of small and dense LDL particles, a common component of the so-called metabolic syndrome (along with high blood pressure). and high blood glucose, and abdominal obesity), which confers a higher cardiovascular risk (CVR) and of developing DM.

Although there is no definitive evidence of their etiological role (they could play an intermediate marker role, being a more distal risk factor in the pathogenic chain), prothrombotic factors (fibrinogen), inflammatory factors (C-reactive protein), homocysteine , etc. Great importance is currently attached to psychosocial factors, such as low socioeconomic status, social isolation, depression or hostility, and work or family stress; in addition to being associated with a higher CVR, these factors worsen the prognosis of patients with established ischemic heart disease and significantly hinder the control of classic CVRFs.




*Cardiovascular risk assessment models*




*The global environment of cardiovascular disease*

## POLYPILL CONCEPT

"Polypill" describes a fixed-dose combination pill that contains several components designed to reduce several cardiovascular risk factors simultaneously. [3,4]

Since the use of aspirin there has been a trend to treat each risk factor rather than the overall risk of the disease. For example, until recently, statins were prescribed only if serum cholesterol was elevated. Medications to lower blood pressure are given only if a diagnosis of hypertension has been made. This means that many people do not receive preventive treatment. [5,6]

The rationale for preventing clinical cardiovascular disease with a combination of agents is that there is no universally accepted, strict threshold below which there is no risk factor reduction. In fact, cohort (prospective observational) studies show that blood pressure and cholesterol exhibit a linear relationship between risk factor level and disease risk when disease risk is plotted on a proportional (logarithmic) scale. ). This relationship is of great clinical importance, because it shows that for changes in risk factor there is a constant proportional change in disease risk. Thus, for example, a 1 mmol /l reduction in low-density lipoprotein (LDL) cholesterol is associated with an approximate 40% reduction in the risk of suffering an ischemic heart disease

(IHD) event, and a reduction in 10 mm Hg in diastolic blood pressure is associated with an approximate 60% decrease in the risk of stroke. Next, we will make a racconto of the aforementioned difficulties, in sectors of the world with different sociopolitical realities.

## WORLD TRIALS AND FINDINGS

**UNITED STATES, New York Metropolitan Area :**

Cardiovascular disease (CVD) is the leading cause of death among Hispanics and Latinos in the US. [7]

The age-standardized prevalence of CVD risk factors varied by Hispanic/Latino origin; large proportions of participants (80% men, 71% women) had at least one risk factor.

The age- and sex-adjusted prevalence of 3 or more risk factors was higher in Puerto Rican participants (25.0%) and significantly higher (P < 0.001) among participants with less education (16.1%).

In adjusted multivariate models, hypertension and smoking were directly associated with coronary heart disease in both sexes, as were hypercholesterolemia and obesity in women and diabetes in men.

For stroke, the associations were positive with hypertension in both sexes, diabetes in men, and smoking in women. The group is at high risk for future CVD morbidity and mortality as they age.

Evidence also suggests that CVD risk factors and disease rates may vary considerably among Hispanic/Latino groups.

The risk of cardiovascular disease among Hispanic/Latino individuals has been reported to differ by degree of acculturation and length of residence in the United States.

This report expands the Hispanic/Latino health literature by describing the prevalence of 5 important and easily measurable biomedical CVD risk factors (elevated serum cholesterol and blood pressure, obesity, hyperglycemia/diabetes, smoking), adverse profiles risk factors for CVD (combinations of CVD risk factors; i.e., 1 alone, 2 alone, or ≥3 risk factors) and CVD (coronary heart disease [CHD] and stroke) among US Hispanic/Latino adults of various origins. Relationships of socioeconomic status (SES), acculturation, and lifestyle factors with adverse CVD risk factor profiles were examined.

**UNITED STATES, Alabama Underserved Populations:**

A randomized clinical trial to evaluate the effectiveness of a polypill -based strategy in an underserved population of people with a low socioeconomic status – summarized below – made it possible to objectify the benefits of the polypill. [8]

A total of 275 individuals were evaluated longitudinally and prospectively; of them, 60% were women.

The mean age of the participants was 56 years and the population was predominantly black (96%).

About three-quarters of the participants reported having an annual household income of less than $15,000.

Obesity was common; the mean body mass index (weight in kilograms divided by height in meters squared) of the participants was greater than 30, and 43% of the participants had stage 2 hypertension or higher.

The mean estimated 10-year cardiovascular risk was 12.7% overall (12.4% in the polypill group and 13.0% in the usual care group).

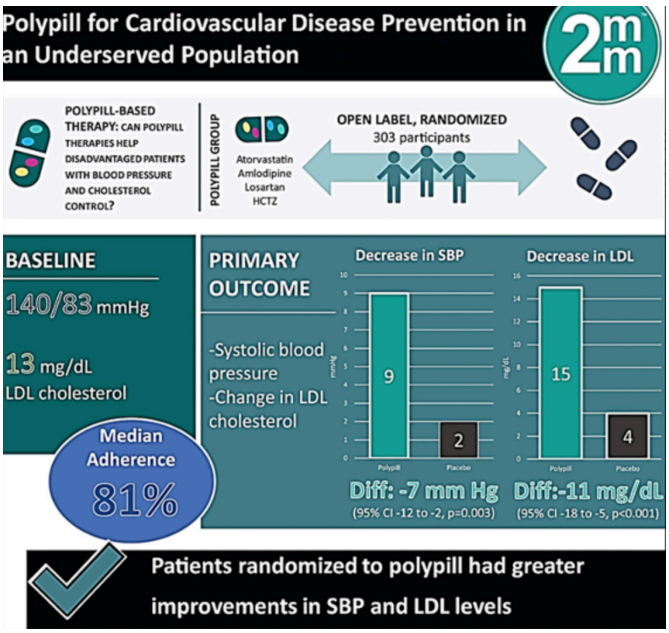
Overall, baseline blood pressure was 140/83 mm Hg and baseline LDL cholesterol level was 113 mg per deciliter (2.90 mmol per liter).

None of the baseline characteristics differed significantly between groups.

In the polypill group , doctors reduced the doses of other antihypertensive or lipid- lowering medications or stopped their use in 44% of patients.

Two percent of participants in the polypill group had an increase in therapy. In the usual care group, none of the participants had a reduction in therapy and 10% required an increase in therapy.

During the trial, there were several serious adverse events related to baseline clinical-pharmacological management: one death due to stroke (in the usual care group) and one case of coronary artery bypass surgery (in the usual care group).




*POLYPILL, MEDICAL RESPONSE AND ADHERENCE*

No participants in the polypill group had abnormal liver function test results.

In this randomized trial, use of a polypill produced greater reductions from baseline in systolic blood pressure and LDL cholesterol than those seen with usual care in a socioeconomically vulnerable minority population.

The observed reductions in systolic blood pressure and LDL cholesterol level were statistically and clinically significant. Based on meta -analyses of trials of cardiovascular outcomes in primary prevention, this study concluded that such changes, if sustained over time, would lead to an approximate 25% reduction in the incidence of cardiovascular events.

This figure is consistent with the 25% relative reduction in estimated cardiovascular risk that was observed among participants who had been randomly assigned to receive the polypill , compared with those assigned to receive usual care.

Adherence in the trial was high, with 91% of participants completing the final trial visit; a noteworthy finding given that approximately half of patients in the United States discontinue their prescribed cardiovascular medications within 1 year.

The simplicity of taking a single pill daily appears to be an important contributor to adherence. In another study, a total of 5,713 participants were randomized and the mean follow-up was 4.6 years, where three cohorts were formed: one with the individual required medications, one with the combined medications in a single polypill, and one with placebo.

Low-density lipoprotein cholesterol was approximately 19 mg per deciliter lower and systolic blood pressure was approximately 5.8 mm Hg lower with the polypill and combination therapy than with placebo.

It was concluded that combination treatment with a polypill led to a lower incidence of cardiovascular events than placebo among participants without cardiovascular disease who were at intermediate cardiovascular risk.

**MIDDLE EAST:**

A systematic review of the literature was conducted by searching the MEDLINE/ PubMed and PARLINE databases between January 1980 and April 2005. Cohort studies published since 1980 that included at least 1000 participants reported prevalence of at least one of the following; diabetes mellitus, obesity (body mass index ≥ 30 kg/m2), hypertension, hyperlipidemia, and smoking in the Middle East region. [9]

In total, 51 studies (267,537 participants) were included.

Based on a random effects model, the overall prevalence of obesity was 24.5%, diabetes mellitus was 10.5%, hypertension was 21.7%, smoking was 15.6%.

Smoking was more common in men than women, while obesity and high blood pressure were more common in women.

The prevalence of obesity and hypertension was higher in women, while the prevalence of smoking was higher in men.

These data suggest that cardiovascular disease will be a major health problem in the Middle East.

**SPAIN:** :

In Spain, a high prevalence of cardiovascular risk factors has been observed together with a low incidence of acute myocardial infarction. [10]

An extensive study aimed to determine trends in the prevalence of cardiovascular risk factors between 1995 and 2005 in the population aged 35-74 years in Girona, Spain. A total of 7571 individuals (52.0% women) were included. Low-density lipoprotein cholesterol > 3.4 mmol /l (130 mg/dl) (49.7%) and arterial hypertension (39.1%) were the most prevalent cardiovascular risk factors.

In 1995, 2000, and 2005, low-density lipoprotein cholesterol decreased in both men and women: 4.05-3.913.55 mmol /l (156-151-137 mg/dl) and 3.84-3.81-3.40 mmol /l (148-147 mg/dl). -131 mg/dl), respectively.

Increases were observed in the consumption of lipid-lowering drugs (5.7-6.3-9.6% in men and 4.0-5.8-8.0% in women), controlled arterial hypertension (14.8-35.4 -37.7% in men and 21.3-36.9-45.0% in women); and obesity (higher for men: 17.5-26.0-22.7%).

The prevalence of myocardial infarction or possibly abnormal Q waves on the electrocardiogram was also significantly increased. [11]

The change in the prevalence of cardiovascular risk factors in Gerona was marked in this decade by a shift to the left in the distributions of total cholesterol and cholesterol bound to low-density lipoproteins, independently of the increased consumption of lipid- lowering drugs , and a better control of hypertension with increased use of antihypertensives.

**INDONESIA:**

The SMARThealth program involves the sustainable development of a mobile-based clinical decision support system to help primary health care workers improve optimal preventive treatment in primary health care. [12]

SMART health Extend – Indonesia was a demonstration project that aimed to determine if SMARThealth can be appropriately and rapidly customized, and then successfully implemented in a rural community in the Indonesian province of East Java.

The program was implemented in Kabupaten Malang in East Java, Indonesia, with trained Primary Care Physicians and non-physician health workers, serving a population of approximately 48,000 subjects.

It focused on increasing the use of effective preventive medications in people at high risk of cardiovascular disease (CVD).

The impact of the program was determined by comparing the results in four intervention villages with those in four control villages.

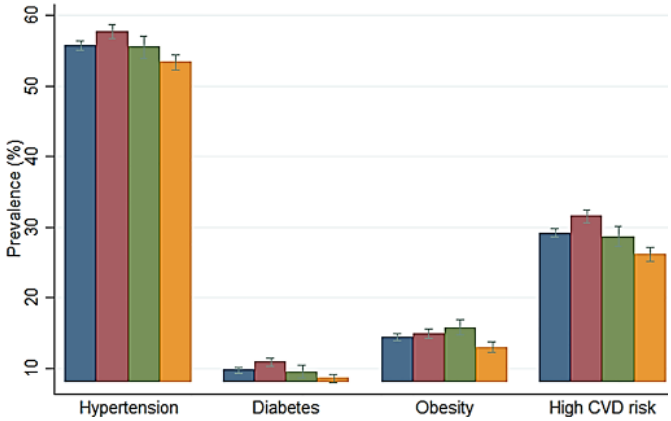
SMARThealth resulted in a significant increase in the use of optimal preventive medication combinations (a blood

pressure-lowering drug together with a statin and aspirin in people with prior CVD) among high-risk people: 15.5% in SMARThealth villages compared with 1.0% in the control villages.

Notably, SMARThealth resulted in large increases in the use of blood pressure-lowering medications in intervention villages compared to control villages (57% compared to 16%), resulting in large reductions in blood pressure .

Malang District government will now embark on a three-year program to expand SMARThealth to all 400 villages in the district.

Technical assistance and evaluation of this expansion will be provided by the research consortium, with funding from the National Health and Medical Research Council (NHMRC)/Global Alliance for chronic Diseases.




*Prevalence of cardiovascular disease risk factors and estimated 10-year cardiovascular risk scores in Indonesia: the SMARThealth study Extend*

## FOCUS PROJECT RESULTS

Adherence to evidence-based cardiovascular (CV) medications after acute myocardial infarction (AMI) is low after the first 6 months. [13]

The use of fixed-dose combinations has been shown to improve adherence to treatment and control of risk factors.

The FOCUS (Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention) cross-sectional study aimed to elucidate factors that interfere with adequate adherence to CV medications for secondary prevention after acute myocardial infarction. In a multivariate regression model , risk of noncompliance (MAQ <20) was associated with younger age, depression, being on a complex medication regimen, poorer health insurance coverage, and lower level of social support, with consistent findings across countries.

The polypill group showed better adherence compared to the group receiving separate medications after 9 months of follow-up: 50.8% vs. 41%.

Adherence is increased in patients with higher levels of insurance coverage and social support. Compared with the 3 drugs administered separately, use of a polypill strategy met the primary adherence endpoint for secondary prevention after acute myocardial infarction.

## RESULTS OF THE POLYLRAN STUDY:

The PolyIran study was a cohort study with 50,045 participants aged 40 to 75 years from the Golestan province of Iran. [14]

Groups (villages) were randomly assigned (1:1) to a package of nonpharmacological preventive interventions alone (minimum care group) or together with a once-daily polypill tablet ( polypill group ).

Randomisation was stratified into three districts, with the village as the unit of randomisation. A balanced randomization algorithm was used, considering block sizes of 20 and balancing either cluster size or natural log of cluster size (depending on skewness within strata). Randomization was performed at a fixed point in time (January 18, 2011) by statisticians at the University of Birmingham (Birmingham, UK), independent of the local study team.

Non-pharmacological preventive interventions (including educational training on a healthy lifestyle, eg, a healthy diet low in salt, sugar, and fat, exercise, weight control, and abstinence from smoking and opium) were delivered by the team of PolyIran field visits at months 3 and 6, and then every 6 months thereafter. Two formulations of polypill tablets were used in this study.

Participants were first prescribed polypill one ( hydrochlorothiazide 12.5 mg, aspirin 81 mg, atorvastatin 20 mg, and enalapril 5 mg).

Participants who developed cough during follow-up were switched by a trained study physician to polypill two, which included 40 mg valsartan instead of 5 mg enalapril .

The participants were followed for 60 months.

The primary outcome to be studied was the occurrence of major cardiovascular events (including hospitalization for acute coronary syndrome, fatal myocardial infarction, sudden death, heart failure, coronary artery revascularization procedures, and nonfatal and fatal stroke).

The use of the polypill was effective in preventing major cardiovascular events. Medication adherence was high. It was concluded that the polypill strategy could be considered as an additional effective component in the control of cardiovascular diseases, especially in LMICs.

### THE AUSTRALIAN TRIAL:

In Australia, a randomized, open-label trial involving 623 participants from Australian general practices was conducted. [15]

Participants had established CVD or an estimated 5-year CVD risk of ≥15%, with indications for antiplatelets , sta-

tins , and ≥2 blood pressure-lowering medications (combination therapy). Participants randomized to the polypill -based strategy received a polypill containing 75 mg aspirin, 40 mg simvastatin , 10 mg lisinopril , and 50 mg atenolol , or 12.5 mg hydrochlorothiazide.

Participants randomized to 'usual care' continued on separate medications and doses as prescribed by their doctor. Primary outcomes were self- reported combination therapy use , systolic blood pressure, and total cholesterol.

After a median of 18 months, the polypill -based strategy was associated with greater use of combination therapy (70% vs. 47%).

At the end of the study, 17% and 67% of participants in the polypill and usual care groups, respectively, were taking atorvastatin or rosuvastatin.

Provision of a polypill improved self- reported use of indicated preventive treatments.

The lack of differences in blood pressure and cholesterol may reflect limited statistical power of the study, although for cholesterol, the improved use of statins in the polypill group offset the use of stronger statins with usual care.

**THE UMPIRE PROJECT:**

The trial 'Use of a Multidrug Pill In Reducing cardiovascular Events ' (UMPIRE) was the first randomized clinical trial to compare a polypill -based treatment strategy for drug delivery (aspirin, two blood pressure-lowering agents, and a statin ) with usual care among participants with established or equivalent high-risk cardiovascular disease (an estimated 5-year cardiovascular risk of ≥15%, eg, hypertensive patients) in India and three European countries (the United Kingdom, Ireland, and the Netherlands). [16]

In the Fixed Dose Combination (FDC) group, clinicians could use a polypill containing aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg or hydrochlorothiazide 12.5 mg. In the usual care group, treatment continued at the discretion of the physicians. In total, 2,004 participants were randomized in India and Europe.

After a median follow-up of 15 months, the polypill group showed better adherence (relative risk of being adherent 1.33, 95% CI 1.26 to 1.41) with a concurrent clinical mean of 2, 6 mmHg (95% CI 1.1 to 4.0) lower.

Mean systolic BP and 0.11 mmol /l (95% CI 0.05 to 0.17) lower, compared with the usual care group.

## RECENT META-ANALYSIS

Yusuf and Cols. [17], carried out the most extensive meta-analyses on the polypill.

In randomized controlled trials, they concluded that fixed-dose combination therapies reduce a combination of cardiovascular disease outcomes in primary prevention. These strategies substantially reduce cardiovascular disease, myocardial infarction, stroke, revascularization, and cardiovascular death in the primary prevention of cardiovascular disease.

These benefits are consistent regardless of cardiometabolic risk factors .

## CONCLUSIONS

Hypertension is one of the main contributors, if not the most important, to the global burden of morbidity and premature death, which is largely related to cardiovascular diseases.

In recent decades, the number of people with uncontrolled hypertension has increased to approximately one billion.

Even among identified and treated individuals, a large proportion of them do not reach the blood pressure (BP) goals currently recommended in high-income countries.

Most of these individuals have mild (grade I) hypertension without overt vascular disease. However, cardiovascular disease risk factors such as hypertension, dyslipidemia, obesity, and insulin resistance tend to cluster together, leaving these people prone to developing cardiovascular disease.

In the Western world, cardiovascular disease affects half of all people throughout their lives. Most surprisingly, the burden of cardiovascular disease is increasing disproportionately in low- and middle-income countries (LMICs ), where more than 80% of cardiovascular deaths worldwide occur.

In those affected by cardiovascular disease, risk factors such as hypertension modify the risk of recurrence of a major cardiovascular event.

Although rates of hypertension awareness and treatment have improved in recent decades, BP control in secondary prevention has similar limited success to primary prevention. Comparable results have been observed for other risk factors such as dyslipidemia.

To stop the rising incidence of cardiovascular disease it will be necessary to review a potential role of the polypill in the treatment of hypertension.

Therapy to lower blood pressure is one of the cornerstones of cardiovascular disease prevention, as it greatly reduces the risk of cardiovascular disease.

A reduction in systolic BP of 10 mmHg has been shown to reduce the risk of coronary events by 20% and cerebrovascular events by 45% in people without cardiovascular disease.

Similarly, in secondary prevention, the risk of a recurrent coronary event is reduced by approximately 25% and a recurrent cerebrovascular event by 35% for every 10 mmHg of systolic BP. A single hypotensive agent in a standard dose generally lowers systolic BP by 8 to 10 mmHg.

Strategies to improve BP control include rapid switching

from monotherapy to multidrug therapy.

In most people with hypertension, the combination of medications is necessary to achieve adequate reductions in BP.

The rationale for combination therapy lies in an additive reduction in BP when several classes of hypotensive agents are combined.

Furthermore, multidrug therapies at a low therapeutic dose are generally better tolerated than the respective monotherapies at higher doses.

Consequently, recent guidelines recommend polydrug therapy with a combination of two hypotensive agents as initial therapy for most hypertensive patients, although this is known to be associated with decreased adherence and inappropriate prescribing.

If provided in a single pill, in addition to potential synergistic actions, a multidrug strategy could improve patient adherence to medication by reducing pill count and dosing frequency. European guidelines even suggest fixed-dose combinations of BP-lowering medications rather than separate BP-lowering agents due to added benefits on adherence.

Therefore, fixed-dose combination pills are well accepted in the treatment of hypertension.

In addition to hypotensive treatment, antiplatelet and cholesterol-lowering therapy decrease the risk of cardiovascular events.

The term polypill was introduced with the publication of articles by Wald and Law in 2003. They proposed a strategy in which all people aged 55 and over and all people with existing cardiovascular disease would be treated with a single pill containing folic acid , aspirin, statin , and three low-dose hypotensive agents.

By simultaneously addressing multiple cardiovascular risk factors in a low- to medium-risk population, regardless of pretreatment levels, the risk of major cardiovascular events could be greatly reduced.

The concept of a multifactorial, multidrug approach regardless of pretreatment risk factor levels to reduce cardiovascular disease risk could be applied to populations at increased risk of cardiovascular disease, such as patients with hypertension or established cardiovascular disease.

Among people without established cardiovascular disease, there has been a transition in recent decades from treatment recommendations for BP lowering and statins that are based on single risk factors, for example, BP thresholds, to treatment based on in a predicted absolute risk of cardiovascular disease.

In these patients, multiple drugs are generally indicated and the margin of benefit is high. Regardless of baseline low-density lipoprotein (LDL) cholesterol, prescription of a statin reduces the risk of a future event.

The reduction in LDL cholesterol is proportional to the clinical benefits. Regardless of the exact components of the polypills , an FDC pill could be considered a multifactorial gold standard therapy that provides the minimum standard therapy for people at moderate to high risk with additional benefits in adherence.

The primary goal of a polypill strategy would be to reduce the risk of major cardiovascular events and mortality.

Long-term adherence in polypharmacy alone is low, with only 45% adherence to antihypertensive therapy and statin use after 12 months.

Combination pills have been shown to increase this adherence by reducing the number of pills and providing simplicity in treatment. Another great advantage of a polypill with important consequences for access to health care in developing countries is related to low costs and improved accessibility.

By dispensing a single generic pill with multiple antihypertensive agents and a statin for hypertension instead of the individual medications, packaging, dispensing, and pharmacy expenses can be greatly reduced.

Therefore, the polypill concept was proposed as a simple, innovative and cost-effective public health strategy to influence drug accessibility and treatment adherence on a global scale. There are also some drawbacks with a fixed-dose pill (FDC), which means that a polypill strategy may not be applicable to all individuals.

Due to the fixed combinations in a single pill, there is no flexibility to be able to change the class of antihypertensive drugs due to contraindications or unacceptable adverse effects.

In particular, patients with hypertension may primarily stop using an FDC pill with blood pressure-lowering agents due to statin -associated myalgia .

These issues could be addressed in the future by the marketing of several multi-component FDC pills, giving the physician a greater variety of drug classes while retaining the convenience of a polypill.

Additionally, FDC pills with two, three, or four BP-lowering agents and a statin could be formulated for hypertensive patients in order to limit the number of pills while achieving BP goals.

FDC formulations correspond closely to combinations already in widespread use, such as an ACE inhibitor, a thiazide diuretic , a beta-blocker, and a statin.

Generic drugs used as components of an FDC pill have been marketed for many years in the prevention of cardiovascular diseases in both primary and secondary prevention.

It is quite possible that many patients will use the same components as a polypill administered at the same time, although not in a single pill or capsule.

However, in substantial contrast to when using an FDC, each of the individual components in standard clinical

practice is generally prescribed at the discretion of the treating physician for a specific indication and with relative contraindications in mind.

The polypill concept includes promoting the widespread use of multifactorial therapies to reduce cardiovascular risk, regardless of risk factor levels that must demonstrate benefit in trials.

A polypill is generally the best alternative treatment compared to almost no treatment; the polypill has been shown to have beneficial effects on adherence and levels of cardiovascular risk factors, indicating a role for the polypill as an adjunctive treatment strategy in the prevention of cardiovascular disease.

There is a theoretical rationale for a polypill- based treatment in a low-risk population, where imperfect and costly detection is avoided. While the low-risk population has a small absolute risk of cardiovascular events, this population includes the majority of those who will experience cardiovascular events due to the large size of a low-risk group.

Furthermore, with the current rising incidence of cardiovascular disease, there would not be enough doctors and health workers around the world to screen and treat all those at risk. Instead of first targeting lifestyle and pharmaceutical treatment only if necessary, a multifactorial approach to preventing and treating cardiovascular diseases is much more efficient. Although lifestyle modification is natural and safe, it is generally not cheap, simple, or sustainable. The polypill could be an important tool to reduce the risk of cardiovascular disease by simultaneously treating multiple risk factors and not only hypertension 16 .

Data indicate that combination pills can produce significant reductions in risk factors and increase adherence to therapy in the long term.

In general, patients prefer a polypill to separate pills, and the therapy is inexpensive.

Results from ongoing trials further evaluating the efficacy of combination pills in lowering blood pressure and cholesterol levels and the effects on adherence to prescribed medications and clinical outcomes would provide clear evidence on the role of the strategical- long-term polypill - based treatment .

It would also have implications for policy formulation to address primary and secondary cardiovascular preventions globally.

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