REVIEW

The Concept of the Polypill in the Prevention of Cardiovascular Disease

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ABSTRACT

Background: Cardiovascular disease (CVD) is a global epidemic and the largest cause of noncommunicable disease—related death worldwide. The concept of a combination pill, or "polypill," composed of aspirin, antihypertensives, and a statin has been suggested to simplify and improve the prevention and treatment of CVD. Individually, these medications have been shown to effectively modify risk factors of CVD, and a single pill composed of these medications has the potential to conveniently and cost effectively provide additive benefits in relative risk reduction. In particular, the polypill concept presents significant potential for reducing the impact of cardiovascular disease in low- and middle-income countries where populations account for >80% of all CVD-related deaths worldwide. Using a polypill as the primary way to prevent CVD has been proposed as a broad "vaccination" strategy to treat asymptomatic individuals based solely on age or the presence of risk factors.

Findings: Several clinical trials have shown that combination pills are well tolerated and have lower relative risk by as much as 60—70% by moderately reducing blood pressure and LDL-cholesterol. However, uncertainty remains in regards to long-term adherence, cost effectiveness, and "medicalization" of asymptomatic individuals, who account for a large percentage of the world's population. Furthermore, more data regarding CVD outcomes is required to evaluate the widespread use of a polypill in primary prevention.

Conclusion: The use of a combination pill in individuals with overt CVD provides the potential to reduce the "treatment gap" that exists in the secondary prevention of CVD by simplifying treatment algorithms, reducing nonadherence, and improving access to medications in countries lacking adequate healthcare infrastructure. The promising results of completed clinical trials have lead to the approval of polypill formulations (e.g., Polycap, Trinomia®, or Zycad) and several large clinical trials are posed to present new data regarding outcomes and adherence.

Key Words: cardiovascular disease, polypill, prevention, public health

Annals of Global Health 2014;80:24-34

INTRODUCTION: THE INCREASE OF NONCOMMUNICABLE DISEASE AND THE EPIDEMIC OF CARDIOVASCULAR DISEASE

In 2010, the General Assembly of the United Nations adopted Resolution 65/238, which detailed the "Scope, modalities, format and organization of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases."[1] This resolution recognized that noncommunicable disease had become a global epidemic and the most common cause of death worldwide. In 2008, 37 million of the 57 million global deaths were secondary to noncommunicable diseases and it is projected that the number will reach 52 million in 2030.[2] Unlike the well-known communicable diseases such as polio, tuberculosis, or HIV, the prevalence of noncommunicable diseases such as cardiovascular disease (CVD), diabetes, chronic respiratory disease, and cancer, has increased with the modernization of society. Adding to the complexity of this epidemic is the inequitable global burden of disease that places the greatest morbidity and mortality in low- and middle-income countries (LMICs). Although noncommunicable disease was once thought to only be the byproduct of the lifestyle of high-income countries, the rapid globalization and urbanization of LMICs over the past 20 years has allowed the spread of the same lifestyle risk factors found in high-income countries (poor diet, lack of physical activity, tobacco use) to now affect the large, vulnerable, populations of LMICs. This change in lifestyle is creating a significant burden of disease that far exceeds the health

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http://dx.doi.org/10.1016/j.aogh.2013.12.008

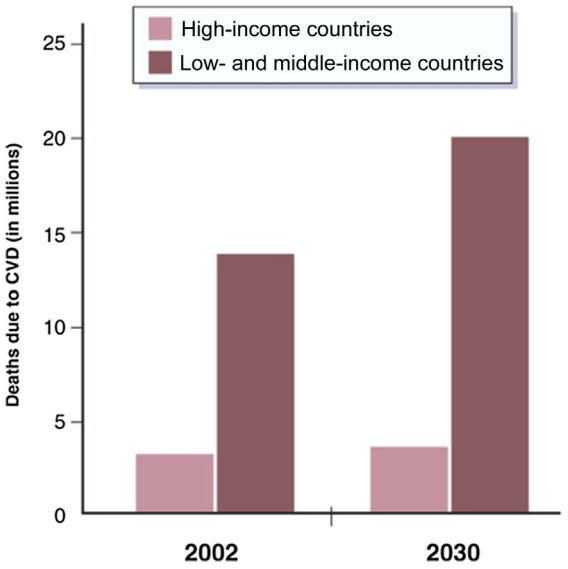

Figure 1. Global CVD mortality. Joshi et al. JACC 2008.

care infrastructure of these economically limited countries. It is now estimated that almost 80% of noncommunicable disease-related death occurs in these economically developing countries and in the next 20 years, noncommunicable disease will cause five times more deaths than communicable disease in LMICs.[2]

Paramount in the increasing effect of noncommunicable disease is the growing prevalence of CVD (heart disease and stroke), which is the largest cause of noncommunicable disease-related death worldwide, accounting for 17 million deaths or roughly 30% of all global death and 39% of deaths in people under the age of 70 years.[2-4] It is estimated that nearly 50% of the global population will suffer from CVD during their lifetime.[3] By 2030 projections indicate that as many as 25 million people will die of CVD.[3] The bulk of this mortality is shifting toward the already vulnerable populations of LMICs (Fig. 1). Although the mortality rate from CVD has declined in high-income countries, the rate has continued to rise in LMICs and it is estimated that >80% of all CVD-related deaths (ischemic coronary heart disease and cerebrovascular disease) now occur in LMICs.[3] In fact the difference in premature death from CVD ranged from 4% in high-income countries to 42% in low-income countries.[5]

In addition to the morbidity and mortality associated with CVD, there is a significant financial cost related to hospitalization, medication, and lost productivity. In 2007, CVD (heart disease and stroke) had an associated cost of $286 billion in the United States[6] and €169 billion ($269 billion) in Europe.[7] The economic effect is perhaps even more severe in LMICs where noncommunicable disease is estimated to reduce gross domestic product by up to 6.77%.[8] CVD-related morbidity and morality depletes the workforce of LMICs and as a result inhibits economic growth, perpetuating a continued cycle of poverty.

CONCEPT OF THE POLYPILL

CVD is a pivotal force driving the detrimental effects of noncommunicable disease. The concept of the polypill is derived from the data that attribute the growth of CVD to modifiable and treatable risk factors that have an inequitable effect on the world's population. Increasing levels of well-established, modifiable risk factors such as obesity, hypertension, dyslipidemia, diabetes, physical inactivity, poor diet, and tobacco use contribute to the CVD epidemic. Large epidemiological studies have shown that these risk factors are pervasive in society and account for as much as 90% of CVD events.[9] In the INTERHEART study 99% of participants had at least 1 CVD risk factor.[9] National Health and Nutrition Examination Survey 2005-2008 data showed that an estimated 76 million adults in the United States have high blood pressure and 33.6 million have total serum cholesterol >240 mg/dL.[6] Globally, the overall prevalence of high blood pressure in adults over the age of 25 years was estimated at 40% and the number of people with hypertension increased from 600 million to 1 billion in 2008.[5,10] Hypercholesterolemia has reached epidemic levels with a global prevalence of 39%.[10] Although CVD risk factors are widespread in society, the prevalence varies with income level and populations of LMICs carry a tremendous burden of these risk factors. This socioeconomic trend is even demonstrated in the United States where the prevalence of risk factors varied based on income. Households with incomes >$50,000 had the lowest prevalence of multiple CVD risk factors (28.8%) and those from households with income <$10,000 had the highest (52.5%).

The traditional approach to the prevention of CVD has been through a process of screening of individuals to identify risk factors and then use behavioral modification combined with pharmaceuticals to improve risk profiles either before manifestation of clinical disease (primary prevention) or after a primary CVD event (secondary prevention). This personalized approach to treating CVD requires a strong health care infrastructure and a patient population that is able to pay for the costs associated with screening tests and the multiple medications required to treat each risk factor. The efficacy of this paradigm of care is dependent on multiple variables, including physician adherence to guidelines, patient adherence to therapy, and the affordability of care. Although this method has been modestly successful at decreasing CVD mortality in high-income countries such as the United States, it has failed to control the growth of CVD on a global level.

Thus, Wald and Law introduced the concept of the polypill in 2003 as a radical new method for the prevention and treatment of CVD.[11] Their idea focused on the development of a single pill composed of fixed combinations of medications that have each individually been shown to effectively treat modifiable risk factors of

Theoretical Effect of Polypill on ischemic heart disease (IHD) and stroke after two years of treatment calculated by Wald and Law [11]
(adapted from Wald NJ and Law RL. BMJ 2003)

Risk Factor	Agent	Reduction in Risk Factor	% reduction in risk (95% CI)	
			IHD	Stroke
LDL Cholesterol	Statin^	70mg/dL	61 (51-71)	17 (9-25)
Blood Pressure*	Three different classes of antihypertensives at half standard dose	11 mmHg diastolic	46 (39-53)	63 (55-70)
Thrombosis	Aspirin (75 mg/day)	---	32 (23-40)	16 (7-25)
Serum homocysteine#	Folic acid (0.8mg/day)	3µmol/L	16 (11-20)	24 (15-33)
Combined effect			88 (84-91)	80 (71-87)
Combined effect# (omitting folic acid)			86	74

*thiazides, β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and calcium channel blockers
#Folic acid omitted based on HOPE-2 trial results[17]
^Atorvastatin 10mg, simvastatin or lovastatin 40mg taken in the evening or 80mg taken in the morning

Figure 2. Theoretical Risk Reductions with Use of Polypill. Wald NJ, Law RL. BMJ 2003.

CVD. They reasoned that this universal pill (composed of a statin, 3 blood pressure medications each at half standard dose, folic acid, and aspirin) would reduce ischemic heart disease events by 88% and strokes by 80%, if taken by everyone over the age of 55 (regardless of risk profile) and everyone with existing CVD (Fig. 2).[11] They argued that the polypill concept was so robust that omission of a single component did not change the risk reduction significantly. For example, omitting folic acid only lowered the calculated risk reduction to 86% for myocardial infarction (MI) and 74% for stroke. The authors calculated their conclusions for total risk reduction by multiplying the relative risks associated with changing each risk factor (blood pressure, cholesterol, platelet function, serum homocysteine) as determined by various meta-analyses. Furthermore, they advocated for using age as the only discriminating factor for treatment because the relative risk for CVD events increases linearly with age and, as a result, the majority of CVD events occur in those over 55 years of age.[11,12] They argued that focusing treatment on those with the most extreme risk profiles would identify only about 15% to 24% of disease events, because on a population level, the majority of events occur in those individuals with values in the middle of risk-factor distribution curves.[11,12] This concept proposed a shift in the paradigm of the prevention and treatment of CVD toward a more simplified, public health-orientated concept. This ideology has been termed the *vaccination strategy* for the prevention of CVD.[12]

SELECTION OF DRUGS FOR A POLYPILL

The selection of the drugs to be included in the composition of the polypill is based on data from multiple clinical trials evaluating the treatment of known modifiable risk factors for CVD. Over the past 20 to 30 years, there have been multiple studies showing the benefit of therapy targeting blood pressure, platelet activity, and lipid levels in reducing the risk for MI, stroke, and cardiovascular death. To determine the components of the original polypill, Wald and Law used meta-analysis to calculate the relative risk reduction offered by each individual substrate. They chose modest doses of generic medications in order to decrease both adverse events (AEs) and cost.

The authors used meta-analysis results to suggest that use of lovastatin 40 mg, simvastatin 40 mg, or atorvastatin 10 mg would result in an absolute reduction in low-density lipoprotein (LDL) cholesterol by 37%, which would predict a 52% relative risk reduction in ischemic heart disease and 17% relative risk reduction in stroke.[13]

Wald and Law derived their data for the incorporation of aspirin (50-125 mg/day) using a meta-analysis that was heavily based on relative risk reduction in secondary prevention.[11,14] Therefore, the application of their results of relative risk reduction of 32% in CVD and 16% in stroke in the setting of primary prevention is potentially an overestimation.

Law and authors found in a meta-analysis of randomized controlled trials (RCTs) that the use of any 2 antihypertensive agents (thiazides, β-blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers, calcium-channel blockers [CCBs]) in combination and at half standard dose would reduce diastolic blood pressure (DBP) by 8.6 mm Hg.[15] As a result, the authors predicted that using 3 antihypertensives in combination and at low doses would reduce DBP by 11 mm Hg and thus decrease the risk for ischemic heart disease events by 46% and stroke by 63%.

Wald and Law also included folic acid (0.8 mg/day) citing results of meta-analysis of case-control studies that showed a 0.4 mg/L decrease in serum homocysteine was associated with 16% to 24% decrease in CVD and stroke.[16] However, this theoretical risk reduction was not

realized in the Heart Outcomes Prevention Evaluation 2 (HOPE 2) study, which showed no benefit, in the prevention CVD events, with the use of folic acid in the lowering of homocysteine levels.[17] As a result folic acid has not been included in current polypill formulations that are undergoing clinical trials.

Some of the controversy surrounding the polypill components is related to its use in primary prevention. A recent review[14] examined the current evidence that exists for the components of the polypill in the context of primary prevention. This review focused on the core components of the original polypill proposed by Wald and Law: statins, antihypertensives, and aspirin. In particular, these authors focused on the mixed evidence for the inclusion of aspirin in a polypill used for primary prevention. Although the benefit of aspirin in the context of secondary prevention is well documented, the authors noted the results of the 2009 Antithrombotic Trialists Collaboration that showed an unclear net benefit for aspirin in primary prevention. Although aspirin use resulted in a 12% reduction in serious vascular events, the result was mainly from a decrease in nonfatal MI (0.18% vs 0.23% per year; $P < 0.0001$) because there was no net effect on stroke (0.20% vs 0.21% per year; $P = 0.4$). Any projected benefit was mitigated by increased gastrointestinal and extracranial bleeding in the aspirin group (0.10% vs 0.07% per year; $P < 0.0001$).[18] The authors also noted a Markov model study by Greving and authors that found aspirin to only be cost-effective for the primary prevention of CVD in men aged 75 years or in men 55 to 66 years with at least 2 CVD risk factors. With respect to primary prevention in women, aspirin was cost-effective in women aged 65 years at 5 times increased CVD risk or women aged 75 years with 2 times increased risk for CVD.[19]

The data for statins and antihypertensives are clearer for primary prevention. A Cochrane review that reviewed 14 RCTs, in which 10% or fewer patients had known CVD, found that statins reduced all-cause mortality (relative risk [RR], 0.83; 95% confidence interval [CI], 0.73-0.95) and combined fatal and nonfatal cardiovascular outcomes (RR, 0.70; 95% CI, 0.61-0.79).[20] Furthermore the statins were not associated with significant AEs nor were they detrimental to quality of life.

With respect to antihypertensives in primary prevention, Carey et al.[14] pointed to a large meta-analysis by Verdecchia, which evaluated the use of β-blockers or diuretics versus ACE inhibitors and CCBs. The Verdecchia paper found no difference in the prevention of coronary heart disease between regimens based on β-blockers/diuretics and regimens based on CCBs or ACE inhibitors.[21] In primary prevention of stroke, CCBs had an 8% reduction in odds for stroke compared with β-blockers or diuretics. However, there was no difference between β-blockers, diuretics, or ACE inhibitors in the primary prevention of stroke.[20]

PHARMACEUTICAL DEVELOPMENT OF A POLYPILL

Moving from the theoretical polypill proposed by Wald and Law to the actual pharmaceutical development of a combination pill presents several challenges. The selection of the medications to include in the combination pill is a complex process. Wald and Law suggested a pill composed of 6 different compounds in order to maximize potential benefit. Although the idea of combining so many compounds into a single pill seems ideal, the reality is that the difficulty of manufacturing a combination pill increases with each component. This is due to challenges related to the chemical properties and potential intellectual properties of each substrate (Fig. 3). In addition, from a clinical standpoint, each additional drug presents the possibility for more AEs and thus using too many components could limit the potential patient population. Furthermore, when choosing the components of the pill, the target population of the therapy must be considered because the benefit for some of the drugs varies with respect to use in primary and secondary prevention of CVD. For example, a polypill that targets secondary prevention might favor the inclusion of an ACE inhibitor and β-blocker over a CCB given the known mortality benefit of the former medications in post-MI patients.

In their review, Sanz and Fuster presented a polypill that would target secondary prevention.[22] As a result their polypill includes aspirin (100 mg), simvastatin (40 mg), and ramipril (2.5, 5, 10 mg). The combination pill proposed by the authors would be available with 3 different doses of ramipril to allow for titration. They did not include a β-blocker in their combination pill, citing concerns about needing to increase the number of formulations of the pill to allow for dose adjustments in order to limit side effects. Sanz and Fuster's concern about limiting the number of formulations of the combination pill is well founded because from a technical

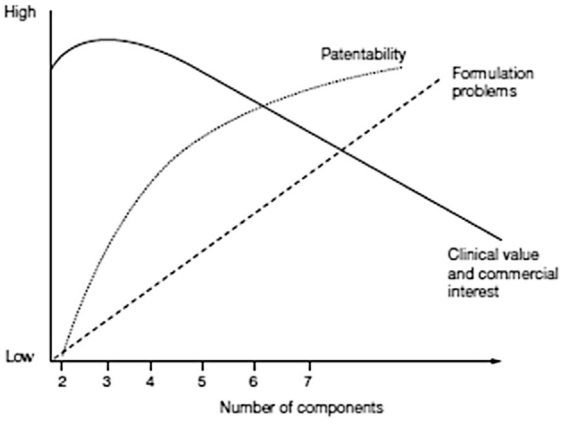

Figure 3. Relationship between the number of drugs in polypill and the formulation challenges, patentability, and clinical value. Adapted from Guglietta A, and Guerrero M.[23]

Company	Polypill	Active Components (mg)
Dr. Reddy's Laboratories (India)	Red Heart Pill 1™	aspirin (75), lisinopril (10), simvastatin (20), atenolol (50)
	Red Heart Pill 2™	aspirin (75), lisinopril (10), simvastatin (20, 40), hydrochlorothiazide (12.5)
Zydus Cadila (India)	Zycad™	aspirin (75), atorvastatin (10), ramipril (5), metoprolol (50)
Alborz Darou (Iran)	PolyIran	aspirin (81), atorvastatin (20), enalapril (5) or valsartan (40), hydrochlorothiazide (12.5)
Zydus Cardia (India)	Ramitorva™	ramipril (5), atorvastatin (10), aspirin (75)
CNIC-FERRER (Spain)	Trinomia®	aspirin (100), simvastatin (40), ramipril (2.5, 5 or 10)
Cadila (India)	Polycap®, Polycap® DS	aspirin (100, 200)simvastatin (20, 40), ramipril (5, 10), atenolol (50, 100), hydrochlorothiazide (12.5, 25)

Figure 4. Developed Polypills. Fuster V. AHA Fellows Presentation 2012.

standpoint there is an almost linear relationship between the number of active components in the polypill and the difficulty of formulation.[23]

The difficulty of formulation relates to the different characteristics of each component with respect to chemical and physical stability. Combining compounds with differing solubility and sensitivity to heat and moisture requires significant development time and cost. The dosages of the different components of the polypill also complicate the development process. The use of certain components in very low doses (such as ramipril at 2.5 mg) combined with another compound at a much higher dose (such as atenolol at 100 mg) causes technical problems with the analytical methods used in purification and bioanalytics.[23] The formulation of a combination polypill also has illustrated the potential for drug–drug interactions and issues with bioavailability. It has been demonstrated that the plasma concentration and bioavailability of simvastatin, when taken as part of the Polycap® pill (simvastatin 20 mg, aspirin 100 mg, hydrochlorothiazide [HCTZ] 12.5 mg, atenolol 50 mg, ramipril 5 mg), was significantly lower than simvastatin taken alone.[24] Paradoxically, the bioavailability of the active metabolite of simvastatin was found to be higher when taken in the combination formulation.

Although the development of a marketable polypill is a complex process, there are several combination pills that have been formulated (Fig. 4).

POLYPILL IN PRIMARY PREVENTION

Although Wald and Law purposed the polypill as a simplified vaccination strategy for the primary prevention of CVD, its use in patients without known CVD has been the source of controversy. Traditionally, the primary prevention of CVD has been focused on each individual patient with a strategy of screening patients to identify those with risk profiles that place them at the highest risk for progression to overt manifestation of disease. This method provides the opportunity for clinicians to practice a personalized form of health care and customize the therapy applied to each individual. Although this approach is favored on the individual level, to be successful it requires adequate health care infrastructure, knowledgeable health care providers, and funding that is often not available in the LMICs that carry a large burden of CVD. Furthermore, Wald and Law claimed that using risk-factor thresholds to determine the initiation of therapy was imprecise because risk increases in a continuous and linear manner.[12] Therefore, choosing to treat only those with high-risk profiles is inadequate because, on the population level, the majority of AEs occur in those individuals whose profiles place them in the middle of risk-factor distributions.[12] Thus, Wald and Law proposed that the algorithm for prevention of CVD should simply use age as the sole risk factor for the decision to treat.[11,12] They argued that age was the only risk factor, on a population level, that provided the largest distribution of relative risk from the bottom to top quantile.[12] They demonstrated that the range of risk for development of CVD increased 130-fold from age 25 to age 75 years, whereas the range of risk from the top and bottom groups in a distribution of blood pressure values only increased 4-fold. Therefore, on a population-based global scale, age is a more effective method to discriminate individuals at risk for CVD (Fig. 5).

The concept of the polypill in primary prevention has been evaluated in several recent clinical trials. The first significant trial evaluating the polypill concept was the The Indian Polycap Study (TIPS). Published in 2009, TIPS was a Phase II double-blind, randomized clinical trial that tested the efficacy, tolerability, and safety of Polycap® (simvastatin 20 mg, aspirin 100 mg, HCTZ 12.5 mg, atenolol 50 mg, and ramipril 5 mg) on 2053

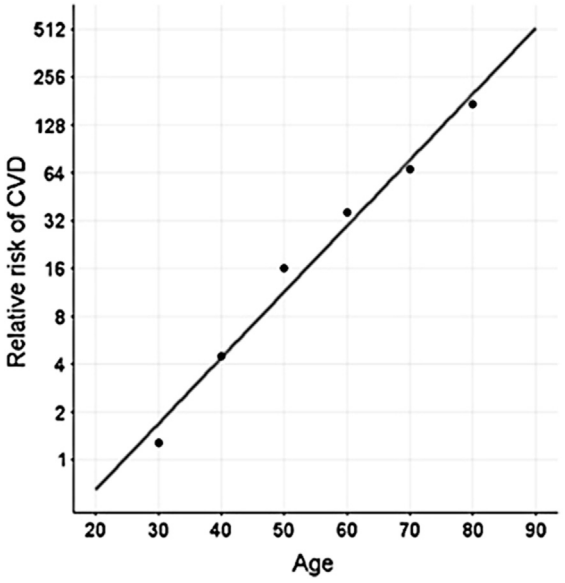

Figure 5. Relative risk of a first cardiovascular disease (CVD) event according to age (based on British data). Adapted from Wald NJ and Wald DS.[12]

individuals in 50 centers in India. This noninferiority study included 9 treatment groups, which received either the Polycap® or the individual components in various combinations over an 8- to 12-week course. The patients had a mean age of 54 years with a single CVD risk factor but without overt manifestation of CVD. The results of the study showed that the Polycap was noninferior to its individual components in lowering blood pressure and heart rate (surrogate of β-blockade). However, Polycap did not reduce LDL levels as well as simvastatin given alone (27 vs 32 mg/dL; $P = 0.04$).[25] This finding could be the result of a lower plasma concentration of simvastatin produced by the Polycap.[14,24] Overall, the discontinuation rates were not significantly different across the treatment groups (16% in Polycap group vs 14.8% overall). The most common reason for discontinuation was patient refusal (9.8% of 14.8% overall) with drug-specific side effects only accounting for 3.8%.[25] Using the same method of calculating relative risks associated with the change in CVD risk factors that Wald and Law used in their seminal paper, the TIPS authors predicted that the Polycap would reduce relative risk of CVD by 62% and stroke by 48%.[25] These values are less than those that Wald and Law predicted for the polypill concept (CVD reduction of 86% and stroke 74%).[11] The lower risk reduction found in the TIPS study is the result of a smaller decrease in DBP (5.6 vs 11 mm Hg) and a more modest reduction in LDL than predicted by Wald and Law. The TIPS authors attributed their findings to lower starting values for blood pressure and LDL in the study group. Also the Polycap used a lower dose statin than advocated by Wald and Law.[25]

In 2010, Malekzadeh and authors published results of their double-blind, RCT of the use of a polypill composed of atorvastin 20 mg, aspirin 81 mg, HCTZ 12.5 mg, and enalapril 2.5 mg. This study, centered in Iran, enrolled 475 patients over the age of 50 years with no history of CVD and followed the cohort for 52 weeks.[26] Unlike the TIPS trial, this study compared the polypill to a single placebo pill. Similar to the TIPS trial results, Malekzadeh's study showed modest reductions in LDL and blood pressure, which led to calculated relative risk reductions that were less than those predicted by Wald and Law (RR of CVD by 44% and stroke by 21%).[26] However, although the polypill was well tolerated with no statistical difference in discontinuation secondary to AEs compared with placebo, there was an estimated nonadherence rate of 30% to 35%. Nonadherence was also an important issue in the trial by the PILL Collaborative. The PILL study was a randomized placebo-controlled trial of a combination dose pill for primary prevention. The use of the combination pill significantly lowered blood pressure (−9.9 mmHg) and LDL-cholesterol levels (0.80 mmol/L) but the discontinuation rate in the polypill group was 23%.[27] Thus nonadherence to medication is a crucial issue when evaluating the true efficacy of a polypill in primary prevention.

The most recent study to evaluate the polypill in the primary prevention of CVD was published in 2012.[27] This double-blind, randomized placebo-controlled, crossover trial investigated the efficacy of a polypill containing amlodipine 2.5 mg, losartan 25 mg, HCTZ 12.5 mg, and simvastatin 40 mg. This polypill (manufactured by Cipla) was given to 86 individuals over the age of 50 years, for a 12-week course, with subsequent crossover to placebo for an additional 12 weeks. The authors were able to produce reductions in DBP of 9.8 mm Hg, SBP 17.9 mm Hg, and LDL of 1.4 mmol/L. These values led to relative risk reductions that were more inline with their original estimates in a 2003 paper (72% in CVD and 64% in stroke).[28] However, it should be noted that the participants in the trial were recruited from patients already taking simvastatin and blood pressure-lowering medications. This method of participant selection could have led to the remarkable adherence rate reported by the authors (98% took more than 85% of their pills) and produced relative risk reduction results that were better than those found in the trials by Malekzadeh and the TIPS authors.[28]

These trials illustrate the potential benefits and current uncertainties associated with use of a polypill in the primary prevention of CVD. All 4 trials showed that use of a combination pill was well tolerated and effective at lowering blood pressure and LDL cholesterol. The calculated risk reduction with respect to CVD and stroke was significant in the trials, although the realized values were less than the theoretical values calculated by Wald and Law in their seminal paper.[11] The studies did illustrate issues with adherence, as illustrated by the nonadherence rate of 30% to 35% in Malekzadeh and authors trial.[26] The results from the Malekzadeh group are particularly important because the study more closely approximates the LMIC population that carries such a high burden of CVD.

Although the trial conducted by Wald et al. had an extremely high adherence rate, this was within a group of individuals from a high-income country that was already taking medications. The nonadherence issue has added relevance given the length of therapy for a combination pill is expected to be life long.

Although these studies seem to support the use of a low-dose polypill for the primary prevention of CVD, there remain several unresolved issues. The first is that the evidence for the universal use of a combination pill for primary prevention is theoretical. To date, there are no results from long-term studies that show actual benefit in morbidity and mortality. However, the ongoing TIPS-3 and Prevention of Cardiovascular Disease in Middle-aged and Elderly Iranians Using a Single PolyPill (POLYIRAN) trials will seek to provide data regarding actual benefit with the use of a polypill in primary prevention with respect to CVD events. The POLYIRAN trial has 3 treatment arms comparing a polypill versus minimal and usual care over a period of 5 years.[29] The TIPS-3 study will follow 5000 participants without known CVD for 5 years and assess the affect of Polycap® (without aspirin) on the rate of CVD events.[30]

Another issue with the primary prevention model involves the uncertainty of medication adherence. Skeptics of the polypill for primary prevention argue that asymptomatic individuals are unlikely to adhere to a lifelong regimen of medical therapy. The high adherence rates cited in the published studies paint an optimistic picture but data regarding long-term adherence rates are lacking. Opponents of the polypill in primary prevention also point toward the lack of solid evidence supporting its cost-effectiveness in people with low or unknown risk factors.[5,31]

Within the health care community there is also concern that the polypill will be viewed as a "silver bullet" in the fight against CVD and as a result, government focus and resources will be directed away from changing the pervasive socioeconomic issues (urbanization, sedentary lifestyle, poor diet, low health literacy, tobacco use) that are driving the CVD epidemic.[32]

Finally, opponents of the use of a polypill in primary prevention cite the possible negative bioethical implications of the "medicalization" of such a large percentage of the world's population. Part of this concern is that the use of medication in the "healthy" and "asymptomatic" will cause these individuals to identify themselves as "patients" with a "diagnosis." This change in self-identification could have significant psychosocial consequences leading to negative repercussions in CVD and society in general.[33]

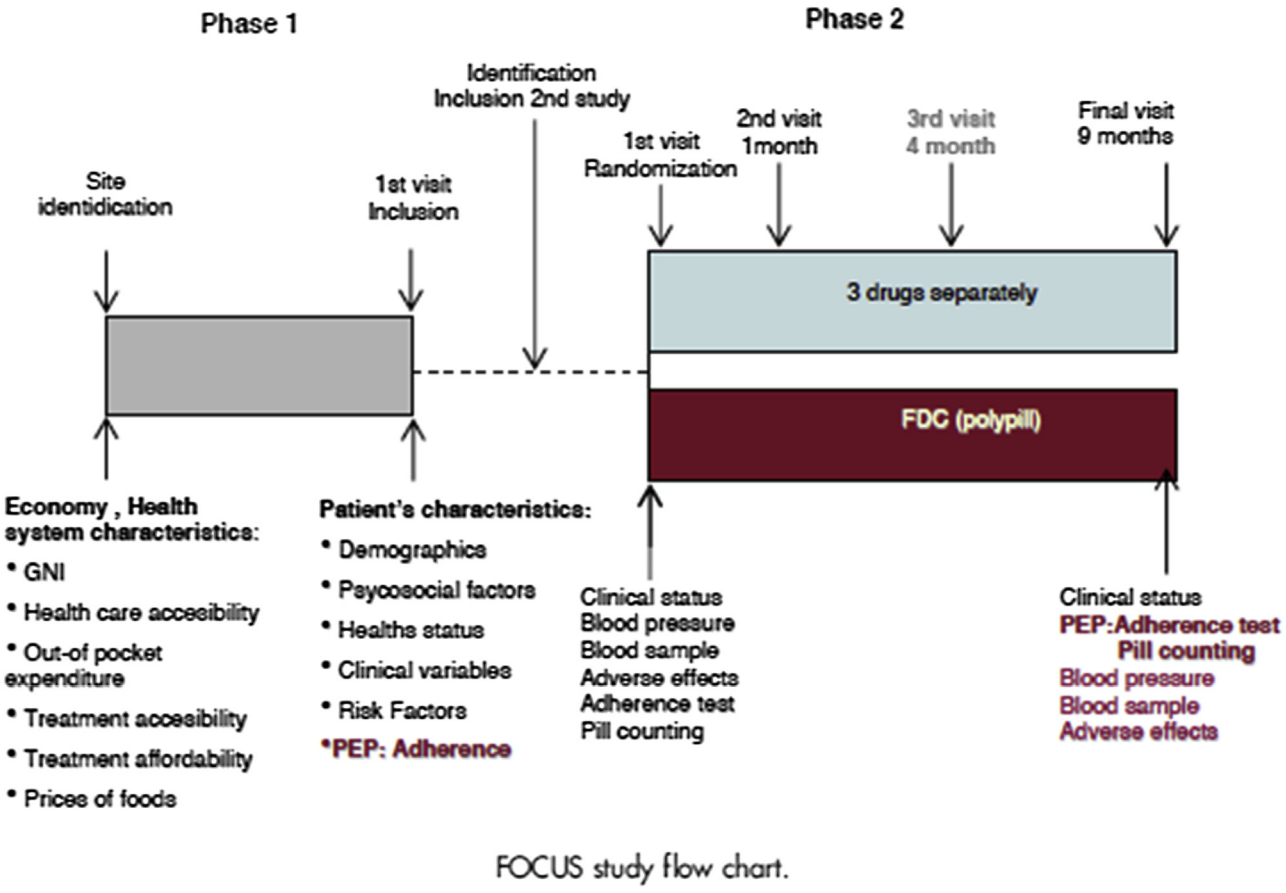

Figure 6. FOCUS study. Sanz G et al. The Fixed-dose Combination Drug for Secondary Cardiovascular Prevention project: Improving equitable access and adherence to secondary cardiovascular prevention with a fixed-dose combination drug. Study design and objectives. (Am Heart J 2011;162:811–817.e1.)

Table II. FOCUS phase 1

- Country economic data
  - Gross domestic product
  - Gross national income
  - Percentage of population below the poverty line
  - Unemployment rate (%)
  - Inflation rate (%)
- Health systems
  - Type of healthcare cover (public/private)
  - Access to medical care
  - Out-of-pocket expenditure
  - Cost of CV drugs
- Population social factors
  - Age distribution and population
  - Literacy rate
  - Educational level
  - Mean salary
  - Cost of basic foods
  - Cost of 1 pack of standard tobacco
- Population health statistics
  - Prevalence of coronary heart disease
  - CV mortality
  - Prevalence of risk factors
  - Availability of medication
    - Percentage of facilities (hospitals, pharmacy offices) in each country in which the medicines are available at the time of survey
  - Affordability
    - No. of days' wages the lowest paid government worker in each country would be required to pay to purchase a 1-month course of medication (4 drugs) from a private source
- Patient characteristics
  - Sociodemographic: age, sex, socioeconomic status, educational level, occupational history, geographic location
  - PHQ-9 (Patient Health Questionnaire 9)
  - Risk factors: diabetes, obesity, hypertension, lipid levels, smoking, family history, and weight and height measures
  - Clinical: AMI date, AMI location, history of congestive heart failure and angina; associated illness (lung disease, renal failure); physical examination: blood pressure, signs of CHF
  - Prescribed medication for CVP: aspirin, statins, ACEIs, β-blockers
  - Psychosocial factors: depression, anxiety, and social support
- Adherence to treatment
  - Morisky-Green test (end point)

Data to be collected. *AMI*, Acute miocardial infarction; *CHF*, congestive heart failure.

Table III. FOCUS phase 2 data to be collected

- Sociodemographic: (see phase 1 variables)
- Risk factors: (see phase 1 variables)
- Clinical data
  - AMI date
  - AMI location
  - History of congestive heart failure
  - Angina
  - Comorbidity (chronic obstructive lung disease, renal failure)
- Physical examination
  - Blood pressure
  - Signs of CHF
- Depression (PHQ-9; Patient Health Questionnaire-9)
- ENRICHD Social support questionnaire (ESSI)
- Twelve-lead ECG
- Blood sample for lipid profile
- Medication provided and returned
- Outcomes
  - Death
  - Reinfarction
  - Rehospitalization for CV cause
- Adherence to treatment (see online Appendix B)
  - Morisky-Green test (end point)
  - Pill count (end point)

Figure 7. FOCUS Data Phase 1 and Phase 2. Adapted from Sanz G et al. The Fixed-dose Combination Drug for Secondary Cardiovascular Prevention project: Improving equitable access and adherence to secondary cardiovascular prevention with a fixed-dose combination drug. Study design and objectives. (Am Heart J 2011;162:811–817.e1.)

POLYPILL IN SECONDARY PREVENTION

The strongest case for the concept of the polypill can be made in the setting of secondary prevention of CVD where the use of aspirin, statins, β-blockers, ACE inhibitors/ARBs have clear benefit as studies have shown that the decline in cardiovascular-related mortality in high-income countries is tied to appropriate medical therapy.[34,35] However, recent clinical trials have demonstrated that the majority of individuals with known CVD still are not reaching the targets for risk-factor reduction. In the recently presented Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial, only 20% of participants achieved goal risk-factor levels after 1-year follow-up. This trend was also seen in results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) and Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluations (COURAGE) trials.[36-38] Therefore, although use of these medications in secondary prevention is fundamental, there are several barriers that have limited their use, causing a "treatment gap" in CVD. These barriers include lack of prescribing of medications by clinicians, accessibility and affordability of medications, and patient adherence to therapy.

The lack of appropriate prescribing of beneficial medications was illustrated in the European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) survey, which showed wide variation in utilization rates for ACE inhibitors and statins in different European countries (ranging from 36% to 95%) in patients with known overt CVD.[39] This treatment gap is further illustrated in the Prospective Urban Rural Epidemiology (PURE) study, which examined the use of medications for secondary prevention, in 153,996 adults with a history of CVD events across countries of

varying wealth. Overall use of appropriate medications was suboptimal (antiplatelet drugs 25.3%, β-blockers 17.4%, statins 14.6%).[40] Perhaps the most notable finding was that the use of appropriate medications decreased linearly with diminishing economic status. As a result, there was a large treatment gap between high- and low-income countries that is most clearly illustrated by the difference in statin use in high-income (66.5%) versus low-income (3.3%) countries.[40] PURE study authors stated that the economic status of the country accounted for two-thirds of the variations in drug use and noted that within all countries, rural settings had the lowest rates of appropriate medication use. The authors cited medication costs, inadequate health care systems, and poor infrastructure (such as transportation systems) as key factors in the disparate treatment results. Proponents of the polypill cite these results in arguing that a single combination pill, given to all patients after manifestation of CVD, could simplify treatment algorithms and increase the ease of providing appropriate medical therapy.

Affordability also plays a large role in the treatment gap. One study found that 1 month of multiple drug therapy could cost between 5.1 and 18.4 days of wages in LMICs.[41] Advocates of the polypill have pointed to Trinomia, (polypill from CNIC-Ferrer), which costs less than 50% of the sum of the prices of its components purchased separately.[42] Furthermore, a Markov model was used in a previous study to demonstrate that a combination pill would be cost-effective in secondary prevention regardless of the socioeconomic level of the target population.[31]

Finally, perhaps the most important factor that affects the effectiveness of secondary prevention is patient adherence to the medication regimen. Appropriate medical therapy for secondary prevention of CVD often requires the individual to take multiple medications. It has been demonstrated that patients who received 4 evidence-based medications after hospitalization for an acute coronary syndrome had significant survival benefit after 2 years compared with patients who only received 1 of these medications.[43] However, adherence has been shown to decrease in proportion to the number of drugs taken by the patient and it is known that adherence to prescription medications can be as low as 40% in patients who were hospitalized for acute coronary disease.[44,45] In chronic coronary artery disease, nonadherence to appropriate medical therapy leads to a 50% to 80% relative increase in risk for mortality.[46] Thus, there is a dilemma in the secondary prevention of CVD because effective treatment often requires several medications, which, negatively affects adherence.

The polypill has been proposed as a logical way to solve this dilemma of adherence in the secondary prevention of CVD. The evidence for the polypill's effect on adherence was evaluated in the Use of a Multidrug Pill in Reducing Cardiovascular Events (UMPIRE) study, which was a randomized trial designed to test the improvement in medication adherence with a polypill compared with usual therapy in patients with established CVD or a calculated 5-year CVD risk of >15%. The study randomized 2004 participants to a combination pill (aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg or HCTZ 12.5 mg) or usual medical therapy over 15 months. The results showed an improvement in adherence of 33% in the polypill cohort with reduction of SBP (−2.6 mmHg) and LDL-cholesterol (−4.2 mg/dL).[47] This result provided actual evidence confirming that the use of a polypill in secondary prevention could improve patient adherence and thus help close the treatment gap in CVD.

The movement for the use of a polypill in secondary prevention will be further advanced by several ongoing trials. The most significant of these trials is the expansive Fixed-dose Combination Drug for Secondary Cardiovascular Prevention (FOCUS) study. This is study is not funded by private enterprise and instead is led by the Centro Nacional de Investigaciones Cardiovasculares (CNIC) in collaboration with research organizations from countries in South America and Europe.[22] The FOCUS study will directly evaluate the use of a polypill in the secondary prevention of CVD through 2 clinical phases (Fig. 6). The first phase is an extensive study of the relationship of the multiple factors (socioeconomic, psychological, clinical) that affect secondary prevention in several countries of differing economic levels (Fig. 7). The primary endpoint of Phase 1 is the assessment of the percentage of patients receiving appropriate medications for secondary prevention and evaluate adherence to treatment.[22] Phase 2 of the FOCUS study will have a primary objective of comparing the adherence rates of 1340 post-MI patients, in 40 clinical sites in South America and Europe, receiving the CNIC-Ferrer polypill Trinomia (aspirin 100 mg, rampril at 2.5, 5, or 10 mg, and simvastatin 40 mg) versus those prescribed the same drugs separately. The secondary endpoints of Phase 2 will involve examining the efficacy, cost-effectiveness, and safety of Trinomia.[22] The concept of the FOCUS study combined with the enormous potential of the polypill has led to the approval of Trinomia in Guatemala, Mexico, and Argentina. Other South American countries are posed to approve the therapy in the near future. Furthermore, Trinomia will undergo FDA review for approval of use in secondary prevention in the United States.

In addition to the comprehensive FOCUS study, there are several other ongoing trials that are evaluating a combination pill strategy in the secondary prevention and populations at high risk for CVD. The Single Pill to Avert Cardiovascular Events (SPACE) is a collaboration of investigators, is conducting several trials in New Zealand, Australia, and Brazil with proposed trials to start in South Africa and China.[48]

CONCLUSION

Noncommunicable disease has become the greatest threat to global public health with CVD being the largest

cause of mortality worldwide.[2] Studies predict that the morbidity and mortality from CVD will continue to increase, with the majority of the burden of disease occurring in LMICs.[2,3] The fight against the epidemic of CVD will require a multifaceted, broad-based strategy that targets core issues at the individual, community, and government levels. One of the issues, contributing to the effect of CVD-related morbidity and mortality, is suboptimal medical treatment of known risk factors in both primary and secondary prevention. This treatment gap can be traced to problems with health care providers (complex treatment algorithms, adherence to guidelines, poor infrastructure), affordability of medications, patient adherence, and accessibility of medications.

The concept of a polypill, composed of a combination of medications that are known to effectively treat CVD, has been proposed as a new method to combat the CVD epidemic on a global scale.[11] This vaccination strategy has been touted as a robust method to simplify the treatment algorithm of primary prevention and lower CVD risk-factor levels on a global population scale. Although several studies have shown the polypill to be well tolerated and noninferior to standard of care,[25,26] there are not yet data showing actual reductions in mortality. Furthermore, questions remain regarding cost-effectiveness, adherence, and the bioethical implications of the "medicalization" of such a large percentage of the world's population.[32,33]

Perhaps the best evidence for the polypill concept is in secondary prevention of CVD where its use has the potential to close the treatment gap that exists. Large trials regarding CVD such as FREEDOM, BARI-2D, and COURAGE have demonstrated that the current treatment strategies for secondary prevention are not effectively improving the risk profiles of those with CVD.[38] Also large epidemiological studies have shown CVD therapy to vary across socioeconomic levels with the worst outcomes in LMICs. The polypill has been proposed as a method to bridge this treatment gap through simplifying treatment algorithms, improving patient adherence, and reducing costs. The World Health Organization, citing positive study results, has recognized the polypill concept as a potential to bridge the treatment gap and named it a "best buy for cardiovascular disease prevention and control" in the setting of secondary prevention (post-MI and stroke).[5] This has led to versions of the polypill, such as Trinomia® and Polycap®, becoming commercially available. In addition, with several additional trials under way (TIPS-3, FOCUS, and SPACE collaboration studies),[49] it seems certain that the polypill will play a large role in the secondary prevention of CVD on a global level.

ACKNOWLEDGMENTS

The authors acknowledge Dr. Martin Goldman for his guidance and contributions.

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