

REVIEW TOPIC OF THE WEEK

A Polypill Strategy to Improve Global Secondary Cardiovascular Prevention

From Concept to Reality

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ABSTRACT

The prevention of cardiovascular disease (CVD) by using a polypill has gained increasing momentum as a strategy to contain progression of the disease. Since its initial conception just over a decade ago, only a handful of trials have been completed assessing the efficacy and safety of this innovative concept. The results of these trials have supported the viability of the polypill in CVD prevention and management, albeit with a few caveats, essentially related to the lack of evidence on the effect of the polypill to effectively reduce cardiovascular events. The polypill has the potential to control the global health epidemic of CVD by effectively reaching underdeveloped regions of the world, simplifying healthcare delivery, improving cost-effectiveness, increasing medication adherence, and supporting a comprehensive prescription of evidence-based cardioprotective drugs. Major trials underway will provide definitive evidence on the efficacy of the polypill in reducing cardiovascular events in a cost-effective manner. The results of these studies will determine whether a polypill strategy can quell the burgeoning public health challenge of CVD and will potentially provide the evidence to implement an effective, simple, and innovative solution to restrain the global CVD pandemic. (J Am Coll Cardiol 2014;64:613-21) © 2014 by the American College of Cardiology Foundation.

Noncommunicable diseases have surpassed communicable diseases as the world's major disease burden, with cardiovascular disease (CVD) remaining the leading global cause of death, accounting for 17.3 million deaths per year, a figure that is expected to grow to 23.6 million by 2030 (Fig. 1) (1,2). The overall aging population (projected to almost double by 2060 in Europe and the United States) (3) and improving survival of patients with coronary heart disease (CHD) have created a large pool of patients eligible for secondary prevention.

The administration of cardiovascular (CV) medications (e.g., statins, antihypertensive agents, anti-thrombotic agents) remains the most common medical

intervention for secondary prevention of CVD, estimated to be responsible for one-half of the overall 50% observed reduction in mortality from coronary artery disease over the past 20 years in some Western countries (4). This tremendous reduction in mortality has been achieved despite patients not receiving the most comprehensive, proven benefit of contemporary medical therapies.

Recent data highlight the massive treatment gap and room for improvement in secondary prevention on a global scale. The PURE (Prospective Urban Rural Epidemiology) study showed that among participants with a history of CHD or stroke, only 25% were taking antiplatelet drugs, 17% were taking beta-blockers,

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ABBREVIATIONS AND ACRONYMS

| | |
|--------------|---------------------------------------|
| BP | = blood pressure |
| CHD | = coronary heart disease |
| CV | = cardiovascular |
| CVD | = cardiovascular disease |
| FDC | = fixed-dose combination |
| LDL-C | = low-density lipoprotein cholesterol |
| LMIC | = low- and middle-income countries |
| MI | = myocardial infarction |
| RCT | = randomized controlled trial |

20% were taking angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and 15% were taking statins 5 years after their event (5). In low- and middle-income countries (LMIC) within the same study, the use of these drugs was as low as 3%. A recent meta-analysis of >375,000 patients estimated adherence to CV medications at 2 years at 57% (6,7).

Rates of compliance with lifestyle modification and adherence to prescribed medications are alarming. More than 50% of patients, on average, decide to abandon their prescribed treatment, and the objectives to improve habits (quit smoking, lose weight,

or engage in physical activity) are met by an equally low or lower percentage (8). Beyond the impact non-adherence has on individual health, it carries a huge economic cost because it is associated with a failure to achieve therapeutic goals, higher rates of hospitalization, and greater incidence of death. Reasons for nonadherence to pharmacological therapy are complex and have been studied in-depth (8-10). Most of the reasons for suboptimal adherence can be grouped into 4 categories: patient-, illness-, provider-, and system-related factors (Central Illustration, Table 1).

Taken together, these considerations lead to ineffective CV prevention and a missed opportunity for reducing CVD. One novel strategy seeking to address adherence is the use of a fixed-dose combination (FDC) polypill. Incorporating the key medications necessary to reduce CV risk into a single, once-daily dose pill could increase use of an effective, inexpensive therapy, thereby lowering costs and improving treatment adherence (11). The concept of the polypill approach was introduced more than a decade ago and has slowly progressed from a conceptual debate to a therapeutic reality. Some of the scientific community's initial skepticism was due to the sweeping proposal from Wald and Law (12), who claimed that a polypill including 6 active components administered to every individual older than 55 years of age would reduce the incidence of CVD by >80%. This "vaccination approach" has never been tested in a large population, and its efficacy, potential adverse effects, and cost-effectiveness would need to be assessed. Subsequently, the indication of the polypill has been suggested in primary prevention, specifically in individuals without previous CVD, with no indication for statins or blood pressure (BP)-lowering drugs, but who are at an overall high risk of CV events. The efficacy of this strategy is currently being tested in 2 large randomized trials. Finally, this third approach, the so-called

"substitution approach," would use the polypill in patients already taking cardioprotective drugs for secondary prevention. The rationale is straightforward: by improving adherence to treatment, availability, and efficiency, the polypill might serve as a strategy to improve risk factor control and ultimately decrease CV events on a global scale (13). Several trials have tested the effect of this adherence approach, with promising results. To date, however, no large randomized controlled trial (RCT) has been conducted to study the effect of the polypill strategy on event recurrence.

CLINICAL DATA/ONGOING STUDIES

Evidence is available on the efficacy, safety, tolerability, and affordability of FDC polypills for the primary and secondary prevention of CVD.

PRIMARY PREVENTION. Several pilot studies have demonstrated the feasibility of the primary prevention strategy (14-17). The large, Phase II randomized TIPS-1 (Indian Polycap Study-1) assessed the effects of different pills containing either single agents or combinations of drugs to measure their effect on risk factors, such as BP and low-density lipoprotein cholesterol (LDL-C) (18). The Phase II study also evaluated the feasibility and tolerability of administering a single pill to a relatively unselected group of patients (characterized by having at least 1 CV risk factor). Patients randomized to the polypill group exhibited BP reductions similar to those assigned to 3 BP-lowering drugs and lower LDL-C reductions compared with those receiving simvastatin alone. Of interest, tolerability of the polypill was similar to that of other treatments, regardless of the number of active components in the 1 pill.

The PILL (Program to Improve Life and Longevity) study reported similar findings in 378 subjects with no indication for any component of the polypill and an estimated 5-year Framingham risk score of >7.5%; they were randomized to receive a polypill containing aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg, and simvastatin 20 mg or placebo for 12 weeks (16). Over 12 weeks, polypill treatment reduced systolic BP by 9.9 mm Hg and LDL-C by 0.8 mmol/l, translating to a 60% long-term reduction in risk for both CHD and ischemic stroke. However, adverse effects (58% in the treated group vs. 42% in the placebo group) and a drug discontinuation (23% in the polypill arm vs. 18% in the placebo arm) were concerning.

Wald et al. (15) tested a polypill containing half-standard doses of 3 antihypertensive agents (amlodipine 2.5 mg, hydrochlorothiazide 12.5 mg, and losartan 25 mg) and a standard 40-mg dose of

simvastatin. In total, 84 individuals with no history of CVD, who were candidates for primary prevention based purely on their age (≥ 50 years), completed the trial. Participants took the polypill for 12 weeks and a placebo for 12 weeks in a random sequence. On the polypill, systolic and diastolic BPs and LDL-C levels were reduced by 17.9 mm Hg (12%), 9.8 mm Hg (11%), and 1.4 mmol/l (54 mg/dl; 39%), respectively. The drug was well tolerated, and no participant experienced a serious adverse event.

Malekzadeh et al. (17) evaluated the effects of a polypill (a quadruple FDC therapy containing aspirin 81 mg, enalapril 2.5 mg, atorvastatin 20 mg, and hydrochlorothiazide 12.5 mg) on levels of LDL-C, systolic BP, and diastolic BP. The study included 50- to 79-year-old Iranian residents (N = 475), without CVD, hypertension, or hyperlipidemia and who were not already taking antihypertensive drugs, statins, or antiplatelet therapy. The patients were assigned either to the polypill or placebo group for 12 months. After controlling for baseline differences, the polypill was associated with modest, yet statistically significant, reductions in BP (4.5/1.6 mm Hg), and LDL-C (8.28 mg/dl) at 12 months. The findings suggest a 34% reduction in CHD risk and a 21% reduction in stroke (28% for total CVD). These modest reductions in BP and lipid levels were less than anticipated (~50% of the expected efficacy) for each of the drugs in the polypill. There were imbalances in baseline characteristics at randomization, and a high rate of drug discontinuation (44% in the combination-pill group and 33% in the placebo group at 12 weeks), which could partially explain the relatively modest risk factor reductions reported. Although the polypill was well tolerated with an 11% discontinuation rate, the consistency of the reported compliance measure was uncertain. The study stressed the need for an adequately powered trial of the polypill for the primary prevention of CVD.

SECONDARY PREVENTION. For secondary prevention, TIPS-2 (Second Indian Polycap Study) reported significant reductions in BP and LDL-C in patients with stable CVD or diabetes with the use of the combination drugs used in TIPS-1. The polypill contained 3 BP-lowering drugs (atenolol 50 mg, hydrochlorothiazide 12.5 mg, and ramipril 5 mg), simvastatin 20 mg, and aspirin 100 mg. In total, 518 subjects eligible for secondary prevention were randomly allocated to receive either a single polypill or 2 capsules of the polypill plus potassium supplementation for 8 weeks. Compared with the single dose, the double dose (or full dose) reduced systolic and diastolic BPs and LDL-C levels by an additional 2.8 mm Hg, 1.7 mm Hg, and 6.6 mg/dl, respectively. Both doses were similarly well tolerated.

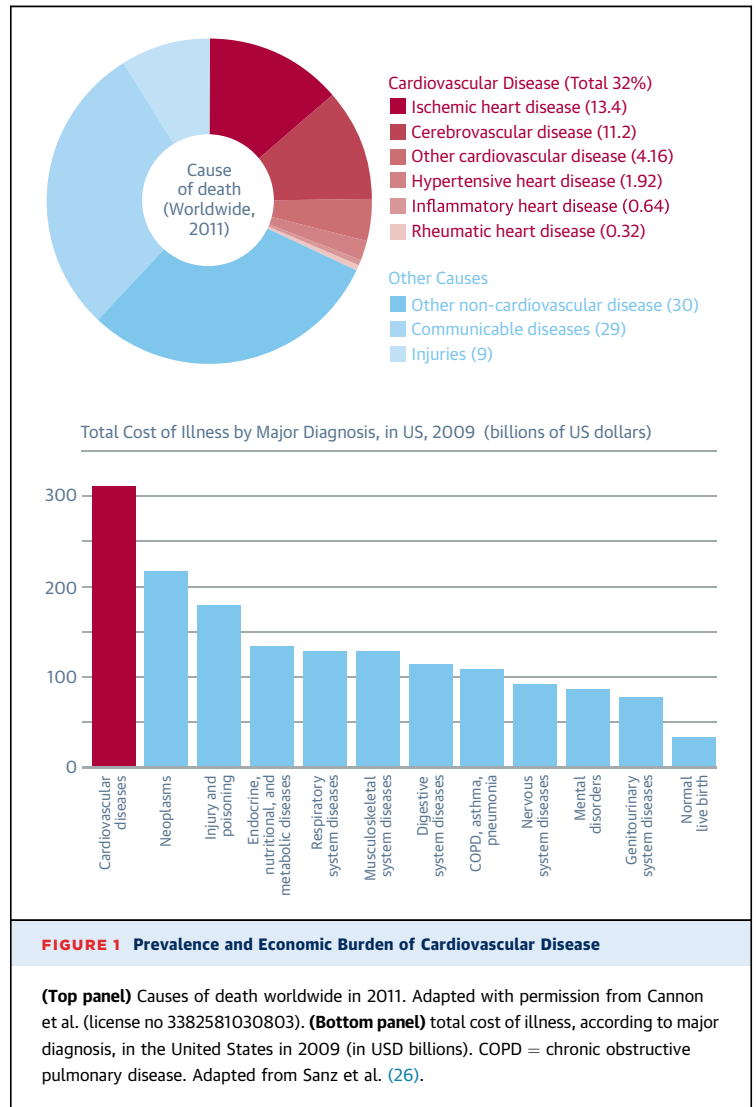
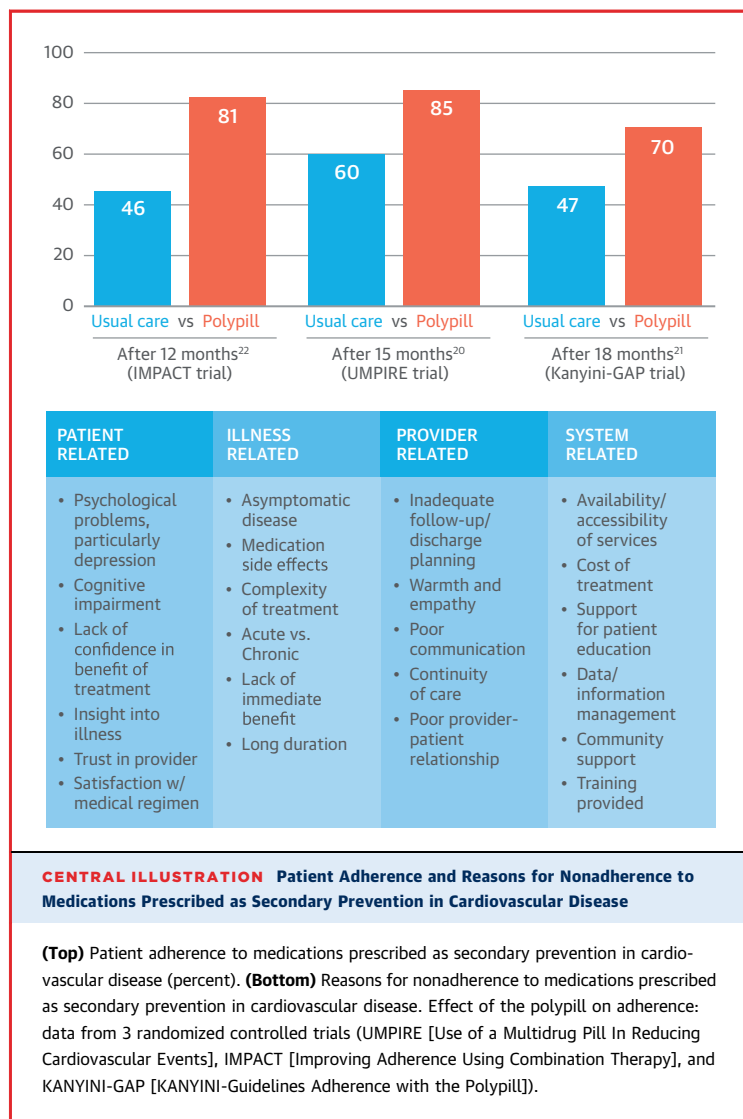


FIGURE 1 Prevalence and Economic Burden of Cardiovascular Disease

(Top panel) Causes of death worldwide in 2011. Adapted with permission from Cannon et al. (license no 3382581030803). (Bottom panel) total cost of illness, according to major diagnosis, in the United States in 2009 (in USD billions). COPD = chronic obstructive pulmonary disease. Adapted from Sanz et al. (26).

The investigators anticipated that the full-dose regimen would reduce the risk of CHD by 75%, and of stroke by 65% (19), if this strategy was used in the primary prevention setting, but they stressed that a large RCT is required to prove this assertion.

The recently published UMPIRE (Use of a Multidrug Pill In Reducing Cardiovascular Events) study was the first randomized trial designed to assess the long-term effect of a FDC strategy in improving patients' adherence to medication in CV prevention (20). Adherence to medication in the polypill group was 85%, compared with 60% in the standard-care group ($p < 0.001$). The study included 2,004 patients (88% with CVD) from 3 European countries and India. Patients were randomly assigned to the FDC (21) strategy or to usual care. Two different FDC strategies were used at the physicians' discretion: aspirin 75 mg, lisinopril 10



treatment (with 2 possible approaches: aspirin 75 mg, simvastatin 40 mg, and lisinopril 10 mg with either atenolol 50 mg or hydrochlorothiazide 12.5 mg) and included 12 months' follow-up. The investigators found that, in line with other studies, adherence to all 4 recommended drugs was greater among FDC than usual care participants at 12 months (81% vs. 46%; relative risk: 1.75 [95% confidence interval: 1.52 to 2.03]; $p < 0.001$) (22).

The latest trial to explore the effect on adherence of the polypill in secondary prevention has just been published and included 623 patients with established CVD or an estimated 5-year CVD risk $\geq 15\%$ (21). After a median of 18 months, patients randomized to the polypill exhibited a significantly higher adherence than those receiving usual care (70% vs. 47%; $p < 0.001$). The study found no significant differences in BP or LDL-C levels between groups, possibly due to the limited power of the study.

ONGOING STUDIES. Several large, ongoing studies are testing the ability of different polypills to reduce the presentation of new CV events in real-world practice. TIPS-3, HOPE-3 (Heart Outcomes Prevention Evaluation-3), PolyIran (Prevention of Cardiovascular Disease in Middle-aged and Elderly Iranians Using a Single PolyPill), and FOCUS studies are currently underway testing a combination pill against placebo.

TIPS-3 will evaluate a preparation of the Polycap without aspirin (either the doses used in the first TIPS trial or enhanced doses based on results of the TIPS-K [Indian Polycap Trial-K] trial) versus placebo over 5 years in 5,000 subjects without CVD and with an estimated risk of major CVD of 1% per year in India and China.

The ongoing HOPE-3 trial is evaluating the concept of combined BP and cholesterol-lowering medications in subjects without vascular disease and with average BP and cholesterol levels (23). The trial is being conducted in 22 countries in North America, South America, Europe, Africa, Asia, and Australia and will soon complete enrollment of 12,500 subjects at moderate risk (men age 55 years and women aged 65 years with 1 risk factor or women aged 60 years with 2 risk factors). Patients are randomized to receive rosuvastatin 10 mg/dl alone, an FDC of candesartan 16 mg/dl and hydrochlorothiazide 12.5 mg/dl alone, both, or neither (2×2 factorial design) for 5 years. The main outcomes will include major CVD events and changes in cognitive and renal function.

The PolyIran study is seeking to determine the effects of a polypill (an FDC of 2 antihypertensive medications, atorvastatin, and aspirin) on primary and secondary prevention of CVD in Iranian adults older than 50 years (24). This ambitious trial will

mg, simvastatin 40 mg, and either atenolol 50 mg or hydrochlorothiazide 12.5 mg. At the end of the study (median follow-up 15 months), adherence to medication in the polypill group was 85% compared with 60% in the standard-care group ($p < 0.001$). BP and LDL-C levels were reduced with the FDC strategy to a greater extent than with standard care, but the differences were modest (2.6 mm Hg and 4.2 mg/dl, respectively; $p < 0.001$ for each). No significant differences were reported in the incidence of serious adverse effects between the groups.

The IMPACT (Improving Adherence Using Combination Therapy) trial evaluated 513 adults at high risk of CVD (with established CVD or 5-year risk of $\geq 15\%$), who were recommended for treatment with antiplatelet, statin, and ≥ 2 BP-lowering drugs, and were randomized to continued usual care or to FDC

TABLE 1 Reasons for Medication Nonadherence

| Patient Related | Illness Related | Provider Related | System Related |
|---|----------------------------|---|--|
| Psychological problems, particularly depression | Asymptomatic disease | Inadequate follow-up/discharge planning | Availability/accessibility of services |
| Cognitive impairment | Medication adverse effects | Warmth and empathy | Cost of treatment |
| Lack of confidence in benefit of treatment | Complexity of treatment | Poor communication | Support for patient education |
| Insight into illness | Acute versus chronic | Continuity of care | Data/information management |
| Trust in provider | Lack of immediate benefit | Poor provider-patient relationship | Community support |
| Satisfaction with medical regimen | Long duration | | Training provided |

divide the cohort into 3 arms: 3,500 randomly selected participants will receive the polypill once daily and minimal care (which consists of direct education and a pamphlet on CV risk reduction, biannual follow-ups, and BP measurements); 3,500 randomly selected participants will receive only the aforementioned minimal care; and 24,000 participants will receive usual care (standard primary health care provided by the local physicians and community health workers for the whole participants of the Golestan Cohort Study, consistent with the current Iranian Health Care System guidelines). The first and second arms will be compared via a 2-arm, open-label, cluster RCT. The comparisons between arm 3 and the other 2 arms will be performed by means of a cohort, multiple RCT design. Endpoints will include major CV events (death and hospitalization).

HOPE-4 (Heart Outcomes Prevention Evaluation-4) is a community cluster RCT that will evaluate an evidence-based program for CVD risk assessment, treatment, and control involving simplified screening and treatment algorithms implemented by nonphysician health workers coupled with lifestyle counseling and combination-pill therapy (25). The initial risk factor phase of the study will assess BP and cholesterol changes in Colombia and Malaysia (50 communities), with plans to expand to 190 communities in 8 countries to evaluate CVD events over 6 years.

The FOCUS project will evaluate the impact of the polypill on patient adherence to treatment. FOCUS consists of 2 separate, prospective phases. Phase 1 is a comprehensive analysis in 5 countries of factors that impede appropriate use of cardioprotective medications. Phase 2 is an RCT, testing the effects of a combination polypill on adherence, BP, and lipids at 9 months in a post-myocardial infarction (MI) cohort (26). The results will be presented this year and will help answer some elemental questions regarding the real impact of the polypill on adherence in a large cohort of post-MI patients, as well as provide a better understanding of the contemporary barriers to cardioprotective medication adherence in secondary

prevention. The designs of the major trials using the polypill are included in Table 2.

ECONOMIC BURDEN OF DISEASE AND COST-EFFECTIVENESS STUDIES. The economic impact of CVD in 2009 was estimated at €196 billion in Europe (27) and \$313 billion in the United States, representing around 17% of overall national health expenditures in the United States, with direct healthcare costs making up approximately 61% (28). The U.S. economic burden of diseases according to major diagnosis is depicted in Fig. 1. In a U.S. retrospective analysis of healthcare insurance claims of adults hospitalized for acute coronary syndrome between 2003 and 2006, the cost of the index acute coronary syndrome hospitalization was \$27,101, which was 49% of the total annual healthcare costs. Prescriptions accounted for a small proportion of all costs; the mean cost of CV prescriptions was \$2,337 (29).

Medication nonadherence results in a huge medical and economic burden, carrying responsibility for 194,500 deaths per year in Europe, leading to an estimated cost of €125 billion annually in Europe and \$300 billion annually in the United States (30). The results of a systematic review studying the impact of medication adherence on coronary artery disease costs and outcomes have recently been published. The authors concluded that high adherence to CV medication significantly improves healthcare outcomes and reduces annual costs for secondary prevention of coronary artery disease (between \$294 and \$868 per patient, equating to 10.1% to 17.8% cost reductions between high- and low-adherence groups) (31). The results of this systematic review underline the potential for a strategy that increases adherence to improve outcomes and cut costs.

Different pharmacoeconomic models all have generally concluded that secondary prevention is highly cost-effective. In this regard, Ito et al. (32) evaluated the comparative cost-effectiveness of interventions to improve adherence to evidence-based medications among post-MI patients. Sensitivity analyses showed that, among the different

TABLE 2 Fixed-Dose Combinations in CV Prevention Studies

| | Population | Polypill Composition | Outcomes | Status |
|---|---|---|--|---|
| Primary prevention | | | | |
| TIPS (Indian Polycap Study), N = 2,053; Yusuf S, Pais P (18) | Men and women aged 40-80 yrs without CVD and with at least 1 CV risk factor in India | Aspirin 100 mg, simvastatin 20 mg, ramipril 5 mg, hydrochlorothiazide 12.5 mg, atenolol 50 mg | Feasibility; effect on risk factor levels; safety and tolerability | Completed |
| PolyIran (Phase II Study of Heart Polypill Safety and Efficacy in Primary Prevention of CV Disease), N = 475; Marshall T, Malekzadeh R, Malekzadeh F (17) | Men and women aged 50-80 yrs without indications or contraindications for aspirin, BP-lowering drugs, and statins in Iran | Aspirin 81 mg, hydrochlorothiazide 12.5 mg, enalapril 2.5 mg, atorvastatin 20 mg | Effect on risk factor levels; safety and tolerability | Completed |
| Combination Therapy Trial, N = 200; Furberg C, Mendis S, Soliman EZ (14) | Age >40 yrs without CVD and with estimated 10-yr total CVD risk score >20% in Sri Lanka | Aspirin 75 mg, simvastatin 10 mg, lisinopril 10 mg, hydrochlorothiazide 10 mg ("red heart pill 2b") | Effect on estimated 10-y total CVD risk score | Completed |
| IMPACT (Improving Adherence Using Combination Therapy), N = 497; Rodgers A, Selak A (16) | Established CVD or 5-yr risk ≥15% | Aspirin 75 mg, simvastatin 40 mg, and either atenolol 50 mg or hydrochlorothiazide 12.5 mg | Effect on adherence to recommended drugs and mean change in BP and LDL-C at 12 months | Completed |
| TIPS-3 (Indian Polycap Trial-3), N = 5,000; Yusuf S, Pais P, Xavier D, Liu L (18) | Primary prevention with estimated yearly CVD event rate of >1% using the INTERHEART risk score in China and India | Polycap; dose to be chosen after completion of the TIPS-K (Indian Polycap Trial-K) trials | Major CVD events; neurocognitive function | Estimated study completion date: January 2019 |
| HOPE-3 (Heart Outcomes Prevention Evaluation-3) (23) N = 12,500; Yusuf S, Lonn E | Primary prevention in men aged >55 yrs and women age >65 yrs with at least 1 CV risk factor and women age >60 yrs with at least 2 risk factors and with average BP and cholesterol levels in 22 countries | Rosuvastatin 10 mg, candesartan 16 mg/hydrochlorothiazide 12.5 mg (2 × 2 factorial design) | Major CVD events; neurocognitive function; renal function | Estimated study completion date: March 2016 |
| Secondary prevention | | | | |
| FOCUS Trial in Secondary Prevention; Phase 1, n = 2,000, Phase 2, n = 800; Fuster V (26) | Survivors of myocardial infarction in Spain and Latin American countries | Aspirin 100 mg, simvastatin 40 mg, ramipril 2.5, 5, or 10 mg (Trinomia) | Adherence; feasibility; effect on risk factor levels; safety and tolerability | Estimated study completion date: June 2014 |
| UMPIRE (Use of a Multidrug Pill In Reducing CV Events) (20) N = 2,000; Thom SA, Rodgers A | Established CVD or high-risk primary prevention (5-yr CVD risk of >15%) in India, the Netherlands, United Kingdom | Aspirin 75 mg, atenolol 50 mg, simvastatin 40 mg, lisinopril 10 mg ("red heart pill 1") or aspirin 75 mg, hydrochlorothiazide 12.5 mg, simvastatin 40 mg, lisinopril 10 mg ("red heart pill 2") | Adherence; effect on risk factor levels; safety and tolerability; CVD events (secondary outcome) | Completed |

BP = blood pressure; CV = cardiovascular; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

interventions, the polypill when combined with mailed education could potentially be a cost-saving strategy if its monthly costs decreased to less than \$100 per patient.

CVD remains the most common cause of death in all developing countries (excluding sub-Saharan Africa, where it is the second) (33). Despite the proven benefits of cardioprotective drugs, these effective, inexpensive treatments are largely underused in developing countries, even in secondary prevention. In addition, industry standards producing generic drugs are not always guaranteed. The proposition of the FDC polypill is that by using a polypill containing components with proven efficacy, its availability and adherence would increase, rendering the polypill a

much-needed efficient strategy to prevent CVD in LMIC.

The cost-effectiveness of a polypill regimen for patients at high risk for CVD specifically in the setting of LMIC has also been tested. Gaziano et al. (34) performed a pharmacoeconomic study assessing 2 combination regimens, 1 for primary prevention (which included aspirin, a calcium channel blocker, an angiotensin-converting enzyme inhibitor, and a statin) and another for secondary prevention (which included the same combination of drugs in group 1 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 a cost-effective intervention for patients with CVD in all developing regions, even in low-income countries.

THE CNIC-FS-FERRER POLYPILL PROJECT: FROM CONCEPT TO REALITY

The Centro Nacional de Investigaciones Cardiovasculares (National Center for CV Investigations [CNIC]), together with Ferrer Internacional, has developed a once-daily polypill for secondary CV prevention, consisting of acetylsalicylic acid 100 mg, simvastatin 20 mg, and ramipril 2.5 mg/5 mg/10 mg (26). Each component of the combination has a well-proven efficacy to prevent recurrence of CV events, and the dosages selected for inclusion are based on achieving the best balance between efficacy and safety. The CNIC-FS-Ferrer polypill is now approved and being commercialized in Guatemala, Mexico, Nicaragua, Dominican Republic, Argentina, Honduras, and El Salvador. A second formulation (consisting of acetylsalicylic acid 100 mg, atorvastatin 20 mg, and ramipril 2.5 mg/5 mg/10 mg) has been approved by various agencies in Europe. This polypill has been developed within a very clear conceptual frame to improve adherence, accessibility, effectiveness, and therefore cost-effectiveness, and has been extensively tested in preclinical and clinical studies, including the aforementioned FOCUS study.

A GLOBAL SCENARIO FOR A POLYPILL STRATEGY

The public health benefits of the polypill could potentially carry a worldwide impact, providing a viable solution to a growing global health concern. Currently, there are 2 global scenarios in which the polypill could be used, for different reasons. First, in a setting of high-income countries, we are experiencing the “CVD paradox” (35), in which worldwide, all-cause mortality declined and life expectancy increased by 9 years between 1979 and 2004 (36). Age-related CVD mortality has also been declining over the past 25 to 30 years, mainly due to risk factor reductions and treatment of established disease (each accounting for approximately 40% to 60% of the decline in CVD mortality). Despite groundbreaking advances in technology and treatment and reductions in age-related CVD deaths, unless the incidence of CVD decreases in accordance with the decline in mortality over the next 20 to 30 years, we will experience a rise in the prevalence of CVD. Second, 1 in 3 Americans (36.9%) currently suffer from some form of heart disease, including hypertension,

CHD, heart failure, stroke, and other conditions. It is projected that by 2030, approximately 116 million people in the United States (40.5%) will have some form of CVD (37). Healthcare costs are increasing worldwide, mostly because of the use of important but expensive new technologies and treatments, but also as a result of people surviving for longer and therefore requiring more health care (including hospitalization) (38) over their lifetime. The cost associated with treating CVD has risen dramatically, and it is predicted that between 2010 and 2030, the cost of medical care for heart disease (in 2008 dollar values) will triple, rising from \$273 billion to \$818 billion (37). Moreover, heart disease also will cost the nation billions more in lost productivity, increasing from an estimated \$172 billion in 2010 to \$276 billion in 2030.

It has become clear that to avoid a decline in the quality of life and avoid the increasing cost of technologies and therapies to treat CVD, we must focus on efficient strategies that promote CV health and prevent CVD. Nearly 30% of all heart attacks that happen in the United States every year are recurrent events (38). CVD prevalence worldwide is expected to further increase as a result of the epidemic of obesity and its consequences, including diabetes, hypertension, and dyslipidemia. Hence, in the setting of developed, wealthy nations with high accessibility to care, the FDC polypill is expected, with the upcoming data from ongoing clinical trials, to significantly increase the effectiveness of CV medications largely by improving adherence levels and, therefore, reducing indirect and direct costs.

Nevertheless, CVD does not affect the world homogeneously: indeed, 80% of CVD deaths occur in LMIC (39). Healthcare systems in these countries often do not allow for robust health care, making it more challenging to combat CVD. Often, there is a severe shortage of physicians, healthcare practitioners, financial means, clinics, medicine, and follow-up care (40). At present, there is no consensus regarding for which patient population the polypill should be prescribed. Although emerging data will help refine indications for the polypill, it is possible that these indications may be broader in LMIC settings. For such a strategy to be effectively implemented, it is critical that the consensus should consist of a few selected criteria, thereby substantially simplifying treatment algorithms to reach the majority of patients at risk for CVD. The polypill is administered as a simple, 1-pill-per-day regimen, with no substantial tolerability issues or monitoring requirements. In addition, it can be distributed as a cost-effective alternative to its multi-pill

counterparts. In this scenario, the healthcare systems of LMIC, which do not have the means to ensure adequate patient services, can adopt the polypill strategy because patients should be able to manage it autonomously.

In settings with fewer resources, a polypill strategy is potentially critical considering that a 1-month supply of standard generic secondary prevention medications can cost a government worker in a low-income country approximately 1.6 to 18.4 days of work wages (40). From a business model point of view, one of the major appeals of an FDC polypill is the use of low-cost mature drugs in an efficient manner. This process increases availability to treatment and renders the polypill as part of an integral strategy to reduce CVD morbidity and mortality in LMIC, which typically cannot afford the huge losses in human and financial resources that result from this disease.

CHALLENGES AND FUTURE DIRECTIONS

There are impressive, potential benefits that come with the use of a polypill strategy in CV prevention. Unfortunately, the use of a polypill for CV prevention is relatively novel, and although data from clinical trials are accumulating, the clinical question that remains to dissipate skepticism is whether the polypill, beyond improving adherence and risk factor control as surrogate markers, can significantly reduce CV events. The polypill has its own share of controversy due to the initial, vaccination strategy proposed by Wald and Law (12), which has never been proven and of which the safety and feasibility remain largely unknown. Skeptics also are concerned that patients will regard the polypill as an excuse to potentially replace efforts to promote healthy lifestyles. The reasoning is that if patients assume an overvalued outlook on the polypill that will protect them from exposure to all CV risk factors, they may feel that they have the freedom to adopt inappropriate lifestyles without consequences. In this regard, the UMPIRE trial has provided direct randomized data demonstrating that people who knew they were taking a polypill showed no adverse effect on lifestyle measures, such as weight, exercise, or smoking (20).

An FDC polypill should be part of an integral program of secondary CVD prevention including lifestyle modification, which should remain a primary component in the armamentarium of CVD prevention. However, in clinical practice, successful and sustained lifestyle modification is achieved in only a small proportion of patients. Furthermore, nearly one-half of patients with established coronary disease abandon effective treatment after 6 months (8). Thus, from a

public health point of view, we may not have the time or luxury of waiting to assess the effects of lifestyle counseling before resorting to evidence-based drug therapy in high-risk individuals, thereby delaying cost-effective care that has been shown to significantly enhance medication adherence and improve risk factor control. Instead, it is appropriate to initiate lifestyle modification simultaneously with drug therapy because the benefits are complementary and additive for CVD prevention.

CONCLUSIONS

Despite major advances in all fields of CV medicine, CVD remains a prevalent global health issue, with a projected increasing incidence over the next 2 decades. The worldwide increase in life expectancy and the consequential aging of the population will result in more subjects developing CVD and requiring treatment for their condition. Coupled with the improvement in life expectancy in patients with established CVD, the associated high healthcare costs may make provision of modern technology and treatments to such a vast number of people unfeasible. The use of a polypill strategy offers a novel and effective solution for those who have poor access to care and budget constraints, while simplifying healthcare delivery and prescription, improving cost-effectiveness, and supporting completeness of evidence-based prescribing. In nations with limited resources, the polypill may ultimately provide better protection than inefficient, sophisticated care.

The polypill has immense potential, few adverse effects, and robust supportive evidence. Strong, comparable alternatives are sparse. As such, it has received the attention of the Wellcome Trust and the World Health Organization, and is endorsed by the World Heart Federation and other authorities concerned about the inordinate burden of CHD.

Available clinical data support the viability of the polypill in CVD prevention and management but with a few reservations. Studies are being conducted around the world as investigators unite to determine whether it is a viable solution to an epidemic facing every country, race, and community. Gradually, the role of the polypill in CV prevention is being defined. Further research of the polypill is needed, with the collective results having the potential power to change the face of health care across the world.

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