The cardiovascular polypill: clinical data and ongoing studies

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ABSTRACT
Cardiovascular risk modification in terms of comprehensive medical therapy (antithrombotic therapy, lipid-lowering therapy, antihypertensive medication) and lifestyle modification (healthy diet, regular exercise, weight loss, smoking cessation) is the cornerstone of secondary prevention. It is now clear that even in those undergoing PCI or bypass surgery, appropriate lifestyle modification and aggressive medical therapy are paramount for optimizing long-term outcomes. However, what has emerged from studies that examined the role of medical therapy in the context of coronary heart disease is that only ~50% of the patients in these studies are achieving target treatment goals for blood pressure, lipid and glycemic control. Non-adherence is thought to be a very large contributor to this problem; across all health-care categories, non-adherence is estimated to account for $290 billion of annual health-care expenditure in the United States and €1.25 billion in European Union, with poor adherence to CVD medication accounting for 9% of all European CVD events. Socioeconomic factors may have a role in patients’ discontinuing their medications, and a major initiative to combat this problem is the increasing focus on the polypill. The idea of combining numerous medications into a single tablet to reduce CV risk was first proposed more than a decade ago. This combined formulation not only significantly enhances patient convenience and adherence but also drives savings for the healthcare systems. Several randomized clinical trials have consistently demonstrated the effects of polypills on CV risk factors and adherence, and major trials are underway to study the effect on hard clinical outcomes.

Global burden of cardiovascular disease: a call for action

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. The last decade has attested to the rapid globalization of the consumer society, which has profoundly impacted lifestyles and cardiovascular (CV) risk factors at a global scale. The growth of poor eating habits, obesity, and hypertension are relentlessly contributing to the development of an epidemic of CVD, the consequences of which have had the highest toll on low and middle-income economies (LMIC). The immediate consequence of this socio-demographic shift had a landmark in 2010 when the World Health Organization (WHO) reported more than 17 million deaths globally were attributed to CVD, over 80% of which occurred in LMIC [1]. Moreover, global CVD mortality estimates project more than 23.6 million CVD related deaths by 2030 [2]. Ischaemic heart disease and cerebrovascular diseases, the most frequent CVDs, are major causes of disability resulting in 130 million disability-adjusted life years (DALYs) lost in 2010 [1].

In parallel, high income countries, where accessibility to resources is high, are encountering what has been termed as the ‘CVD mortality paradox’ [3], which describes the inverse relationship between CVD mortality and cost. In the US, the death rate from CVD has fallen about 39 percent between 2001 and 2012 [2] as well as in most European countries [4], yet the burden and risk factors remain alarmingly high and the costs of treating CVD in high income countries are staggering. Data from the Heart Disease and Stroke Statistics from 2015 showed that the annual direct and indirect cost of CVD and stroke in the US United States is an estimated $320.1 billion. This figure includes $195.6 billion in expenditures (direct costs, which include the cost of physicians and other professionals, hospital services, prescribed medications, and home health care, but not the cost of nursing home care) and $124.5 billion in lost future productivity attributed to premature CVD and stroke mortality in 2011 (indirect costs) [2]. In other words, CVD and stroke accounted for 15% of total health expenditures in 2011, more than any major diagnostic group [5]. In Europe, the total cost of CVD is estimated at €196 billion a year, of which 54% is due to health care costs,
24% due to productivity losses and 22% due to informal care of people with CVD [4]. Health care costs represent €212 per capita per annum, which is around 9% of the total health care expenditure across the EU. The economic impact of CVD in LMICs has been estimated to reduce gross domestic product by up to 6.77% [6], which has already been impairing economic growth in certain regions.

Optimizing secondary prevention in patients with CVD remains as a big unmet need worldwide. The causes of inadequate secondary prevention are multiple. First, lack of treatment adherence in patients is a serious problem that has been overlooked in recent decades. The problem is most apparent in patients with chronic diseases and has been reported in all countries studied, irrespective of the health care system, economic situation, and education level [7]. Levels of adherence in secondary prevention, irrespective of the assessment tool, have consistently been shown to be about 50% [8,9]. Together with the type of drug, one of the main reasons for treatment discontinuation is its complexity and, particularly, the number of doses (ie, pills, capsules) that the patient must take every day [10]. The problem is bigger in LMIC, where access to the healthcare system may be limited and medical attention deficient. Medication is frequently unavailable or too expensive, given that health care coverage in LMIC is practically nonexistent and drugs in the private sector are expensive. The WHO-PREMISE study found that in some LMICs fewer than 40% of acute myocardial infarction patients received ACEIs, and only 20% received statins [11]. The Prospective Urban Rural Epidemiological (PURE) study included individuals from rural and urban communities in countries at various stages of economic development in order to establish accessibility to CV pharmacotherapy. The study confirmed that adherence with drugs for secondary prevention in patients with established CVD was generally low and worst in the low-income countries; with over 80% receiving none of the effective drug treatments in South Asia [12]. Thus, any attempt to apply individualized medicine in those countries according to our standards is a pipe dream. Despite the efforts of healthcare authorities, professionals, and scientific bodies, the situation in developed countries is still far from ideal. In countries with adequate accessibility to treatment, there is a need to increase effectiveness, which demands improving treatment adherence.

**Evolution of the polypill concept**

Limitations on real world applicability of various public health strategies to influence dietary and physical habits make it unfeasible to have a significant impact in a reasonable timeframe (such as educational efforts, legislation, dietary recommendations, public health system infrastructure to meet preventive needs, etc.). Hence, the concept of the polypill was proposed as a simple, innovative and cost-effective public health strategy to influence accessibility to medications and adherence to treatment at a global scale. For some health professionals, the idea of a polypill for CV prevention is merely an interesting concept that is of limited usefulness and applicability. For others, however, the polypill could save thousands of lives if used in the proper context and with the correct indication. What is clear to most is that the global burden of CVD requires new, simple approaches to impede the growth of CVD by effectively improving quality of care.

The concept of the CV polypill is now more than a decade old. It was originally proposed in 2001 by a WHO and Wellcome Trust expert group [13] and subsequently specified as a combination of four drugs (beta-blocker, angiotensin converting enzyme [ACE] inhibitor, aspirin and a statin), which was estimated to reduce CVD events by 75% in people with clinical evidence of CVD [14]. Reservations about this CV prevention strategy certainly are multifactorial, but a decisive part has clearly been played by the original interpretations of the role of the polypill and its possible indications. In 2003, Wald and Law claimed that a polypill containing six components and administered to each individual older than 55 years, irrespectively of their risk factors status, would reduce the incidence of cardiovascular disease by more than 80% [15]. This “vaccination approach” found strong opposition among the scientific community because of the unknown consequences of medicalizing an entire population, the costs of potential adverse reactions, psychological effects in a healthy population, as well as the possibility of promoting unhealthy lifestyle habits. Without suitable clinical studies demonstrating its efficacy, this strategy is unlikely to gain the acceptance of health care professionals and regulating authorities.

Based on Wald and Law’s initial idea, various authors proposed a more selective use of polyps for primary prevention in individuals without CVD but high CV risk [16]. There is no definitive proof of the efficacy, safety, or cost-effectiveness of this approach, although its feasibility has been shown in several pilot studies [17,18]. Overall, the studies show that the use of a CV polypill significantly increases treatment adherence [19–21]. None of these studies had the power to detect differences in the rate of new coronary events. Therefore, the results of new studies, some currently underway, are required to confirm that the polypill can play a role in the primary prevention of coronary disease.

The use of a polypill strategy has been advocated for secondary prevention in patients with CVD, particularly those who have already had a myocardial infarction [22]. This strategy may improve treatment accessibility and affordability in developing countries and increase treatment adherence, still poor in all socioeconomic levels, which increases subsequent event rates and health care costs. The main strengths of a polypill strategy are the significant beneficial impact on adherence, as shown in numerous randomized clinical trials [9,19–21], and cost-effectiveness, where polypills have been shown to be cost saving for health care systems [23–27]. Therefore, polypill-based strategies for optimizing CV prevention are attractive options both for LMIC and developed countries. In this context, the Fuster-CNIC-Ferrer polypill was developed as a response to the current challenging global scenario of CVD. It is a three-component polypill, comprising aspirin, a statin and an ACE inhibitor, designed for secondary prevention in patients who have already suffered a CV event. This polypill was designed as a key element for a comprehensive public health program of CV prevention, which necessarily must include education of patients and physicians on health promotion and changes in lifestyle.

**From conceptual debate to worldwide reality: clinical evidence supporting the use of a cardiovascular polypill as a public health strategy**

Evidence is available on the efficacy, safety, tolerability, affordability and effect on adherence of polypills for the primary and secondary prevention of CVD. All CV polypills that have been developed before the Fuster-CNIC-Ferrer CV polypill have not achieved the regulatory requirements to be approved in any European country or in USA.

**Primary prevention**

Several pilot studies have demonstrated the feasibility of the polypill-based primary prevention strategy [28–31]. In summary, these randomized trials have shown that the combination
panels, including the WHO and the Combination Pharmacotherapy and Public Health Research Working Group who advocate carrying out research that provides further evidence on the use of a polypill in this area [32–34]. For secondary prevention, TIPS-2 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, that is a polypill containing 3 BP-lowering drugs and at least 1 CV risk factor and, with average BP and cholesterol levels in 22 countries.

Secondary prevention

The potential value of applying the polypill concept for secondary prevention has been recognized by different expert panels, including the WHO and the Combination Pharmacotherapy and Public Health Research Working Group who advocate carrying out research that provides further evidence on the use of a polypill in this area [32–34]. For secondary prevention, TIPS-2 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, that is a polypill containing 3 BP-lowering drugs and at least 1 CV risk factor and, with average BP and cholesterol levels in 22 countries.

Secondary prevention of several antihypertensive agents, a statin, and aspirin can substantially reduce blood pressure and lipid levels (Table 1). The pills were well tolerated and showed low rates of adverse effects and discontinuation. The trials have also shown high adherence rates, although most have studied for short duration.

### Table 1

<table>
<thead>
<tr>
<th>Population</th>
<th>Polypill Composition</th>
<th>Outcomes</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men and women aged 40–80 years without CVD and with at least 1 CV risk factor in India</td>
<td>Aspirin 100 mg, simvastatin 20 mg, ramipril 5 mg, hydrochlorothiazide 12.5 mg, atenolol 50 mg</td>
<td>Feasibility; effect on risk factor levels; safety and tolerability</td>
<td>Completed</td>
</tr>
<tr>
<td>Men and women aged 50–80 years without indications or contraindications for aspirin, BP-lowering drugs, and statins in Iran</td>
<td>Aspirin 81 mg, hydrochlorothiazide 12.5 mg, enalapril 2.5 mg, atorvastatin 20</td>
<td>Effect on risk factor levels; safety and tolerability</td>
<td>Completed</td>
</tr>
<tr>
<td>Age &gt;40 years without CVD and with estimated 10-year total CVD risk score &gt;20% in Sri Lanka</td>
<td>Aspirin 75 mg, simvastatin 10 mg, lisinopril 10 mg, hydrochlorothiazide 10 mg (Red Heart Pill 2b)</td>
<td>Effect on estimated 10-year total CVD risk score</td>
<td>Completed</td>
</tr>
<tr>
<td>Established CVD or 5-year risk ≥15%</td>
<td>Aspirin 75 mg, simvastatin 40 mg, and lisinopril 10 mg with either atenolol 50 mg or hydrochlorothiazide 12.5 mg</td>
<td>Effect on adherence to recommended drugs and mean change in blood pressure and LDL-C at 12 months</td>
<td>Completed</td>
</tr>
<tr>
<td>Primary prevention with estimated yearly CVD event rate of &gt;1% using the INTERHEART risk score in China and India</td>
<td>Polypill; dose to be chosen after completion of the TIPS-K trials</td>
<td>Major CVD events; neurocognitive function</td>
<td>Estimated study completion date: January 2019</td>
</tr>
<tr>
<td>Primary prevention in men aged ≥55 years and women aged &gt;65 years with at least 2 risk factors and with average BP and cholesterol levels in 22 countries</td>
<td>Rosuvastatin 10 mg, candesartan 16 mg, hydrochlorothiazide 12.5 mg (2x2 factorial design)</td>
<td>Major CVD events; neurocognitive function; renal function</td>
<td>Estimated study completion date: March 2016</td>
</tr>
<tr>
<td>Survivors of myocardial infarction in Spain and Latin American countries</td>
<td>Aspirin 100 mg, simvastatin 40 mg, ramipril 2.5, 5, 10 mg (Trinomia)</td>
<td>Adherence; feasibility; effect on risk factor levels; safety and tolerability</td>
<td>Completed</td>
</tr>
<tr>
<td>Established CVD or high-risk primary prevention (5-year CVD risk of &gt;15%) in India, Netherlands, UK</td>
<td>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)</td>
<td>Adherence; effect on risk factor levels; safety and tolerability; CVD events (secondary outcome)</td>
<td>Completed</td>
</tr>
<tr>
<td>Established CVD or high risk primary prevention (5-year CVD risk of &gt;15%) Australia</td>
<td>Aspirin 75 mg, simvastatin 40 mg, and lisinopril 10 mg and either atenolol 50 mg or hydrochlorothiazide 12.5 mg.</td>
<td>Adherence to medications, systolic blood pressure and total cholesterol.</td>
<td>Completed</td>
</tr>
<tr>
<td>Elderly population (&gt;65 years) with a diagnosis of AMI</td>
<td>Trinomia (Aspirin 100, Ramipril 2.5, 5 or 10mg, Atorvastatin 40mg)</td>
<td>Composite primary endpoint of cardiovascular death, nonfatal MI, nonfatal ischaemic stroke and urgent revascularization</td>
<td>Ongoing. Estimated study completion date: April 2020.</td>
</tr>
</tbody>
</table>
the single dose, the double-dose, or full-dose, reduced systolic and diastolic BPs and LDL-C levels by an additional 2.8 mmHg, 1.7 mmHg, and 6.6 mg/dL, respectively. Both doses were similarly well tolerated. The investigators anticipate that the full-dose regimen would reduce the risk of CHD by 75%, and of stroke by 65% [35].

The Use of a Multidrug Pill In Reducing cardiovascular Events (UMPIRE) study was the first randomized trial designed to assess the long-term effect of a polypill strategy in improving patients’ adherence to medication in CV prevention [20]. This trial included 2,004 patients (88% with CVD) from 3 European countries and India. Two different polypill strategies were used at the physicians’ discretion: 75 mg aspirin, 10 mg lisinopril, 40 mg simvastatin, and either 50 mg atenolol or 12.5 mg hydrochlorothiazide. 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-cholesterol levels were reduced with the polypill strategy to a greater extent than with standard care, but the differences were modest (2.6 mmHg 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 trial evaluated 513 adults at high risk of CVD (with established CVD or 5-year risk of ≥15%), who were recommended for treatment with antiplatelet, statin, and 2 or more BP-lowering drugs, and were randomized to continued usual care or to polypill 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 polypill than usual care participants at 12 months (81% vs 46%; relative risk 1.75, 95% CI 1.52-2.03, p<0.001) [21].

Patel et al. recently published the results of an open-label, randomized trial involving 623 participants recruited in Australian general practices [36]. Participants had established CVD or an estimated five-year CVD risk of ≥15%, with indications for antiplatelet, statin and ≥2 blood pressure lowering drugs (‘combination treatment’) and were randomized to the ‘polypill-based strategy’ received a polypill containing aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg and either atenolol 50 mg or hydrochlorothiazide 12.5 mg. Participants randomized to ‘usual care’ continued with separate medications and doses as prescribed by their physician. Primary outcomes were self-reported adherence to medications, systolic blood pressure and total cholesterol. After a median of 18 months, patients randomized to the polypill presented 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 between both groups, possibly due to limited power of the study.

The FOCUS (Fixed Dose Combination Drug for Secondary Cardiovascular Prevention) study was the first to prove the benefits of a polypill strategy in secondary prevention. FOCUS was fully funded by the FP7 EC programme and consisted of a cross-sectional study (Phase 1) of 2118 post MI patients recruited in Argentina, Brazil, Italy, Paraguay, and Spain, aimed to elucidate factors that interfere with appropriate adherence to CV medications for secondary prevention after an AMI [37]. Additionally, 695 patients from phase 1 were randomized into a controlled clinical trial (Phase 2) to test the effect of Fuster-CNIC-Ferrer CV polypill (a polypill containing aspirin 100 mg, simvastatin 40mg and ramipril 2.5, 5 or 10 mg) compared to the three drugs given separately on adherence, blood pressure (BP) and low density lipoprotein cholesterol (LDL-C), as well as safety and tolerability over a period of 9 months of follow-up. Primary end-point in phase 2 was adherence to the treatment measured at the final visit by the self-reported Morisky-Green Adherence Questionnaire (MAQ) and pill count (patients had to meet both criteria for adherence at the in-person visit in order to be considered adherent). The results of phase 1 showed a very low overall CV medication adherence of 45.5%. In a multivariable regression model, the risk of being non-adherent was associated with younger age, depression, being on a complex medication regimen, poorer health insurance coverage, and a lower level of social support, with consistent findings across countries. In Phase 2, the polypill group showed improved adherence compared to the group receiving separate medications after 9 months follow up: 50.8% vs 41% (p=0.019; intention-to-treat population) and 65.7% vs 55.7% (p=0.012; per protocol population) when using the primary endpoint, attending the final visit with MAQ and high pill count (80–110%) combined, to assess adherence. Adherence was also higher in the FDC group when measured by MAQ alone (68% vs. 59%, p=0.049). No treatment difference was found at follow-up in mean SBP (129.6 vs 128.6 mmHg), mean LDL-C levels (89.9 vs 91.7 mg/dL), serious adverse events (23 [6.6%] vs. 21 [6%]) or death (1, 0.2% in each group). In consonance with other clinical trials, compared with the three drugs given separately, the use of a polypill strategy met the primary endpoint for adherence – self-reported and direct measured medication – for post-MI secondary prevention.

Ongoing clinical trials

Several large, ongoing studies are testing the ability of different polypills to reduce the occurrence of new CV events in real-world practice. TIPS-3, HOPE-3, Poly-Iran, and HOPE-4 are currently underway testing different combination pills 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 trial) versus placebo over 5 years in 5,000 individuals without CVD and with an estimated risk of major CVD of 1%/year in India and China. The ongoing HOPE-3 trial is evaluating the concept of combined BP and cholesterol lowering medications in individuals without vascular disease and with average BP and cholesterol levels [38] in 22 countries in North and South America, Europe, Africa, Asia, and Australia and will soon complete enrollment of 12,500 individuals at moderate CV risk (men age 55 years, with women over 65 years with 1 risk factor or women over 60 years with 2 risk factors). Patients are randomized to rosuvastatin 10 mg/day alone, a FDC of candesartan 16 mg/hydrochlorothiazide 12.5 mg/day 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 (a FDC of 2 anti-hypertensive medications, atorvastatin, and aspirin) on primary and secondary prevention of CVD in Iranian adults older than 50 years [39]. This ambitious trial will divide the cohort in 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 will receive only minimal care as described above; 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 Golestan Cohort study, consistent with the current Iranian Health Care System guidelines). The first and second arms will be compared via a 2-armed open-labeled 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 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 non-physician health workers coupled with lifestyle counseling and combination-pill therapy [40]. 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 SECURE trial: comparing the efficacy of the Fuster-CNIC-Ferrer CV Polypill vs. usual care in reducing major adverse cardiovascular events during secondary prevention.

The SECondary prevention of cardiovascUlar disease in the Elderly (SECURE; EudraCT: 2015-002868-17; NCT0259612) study is a multicenter, international, randomized trial designed to evaluate the potential benefit of the Fuster-CNIC-Ferrer CV polypill, containing aspirin 100 mg, ramipril 2.5, 5 or 10 mgs and atorvastatin 40mg as a component of a cost-effective, globally available and comprehensive treatment strategy for secondary CV prevention. SECURE will enroll a total of 3206 patients >65 years old within 8 weeks of a MI to compare the efficacy of this polypill in reducing major cardiovascular events (cardiovascular death, nonfatal MI, nonfatal ischemic stroke, and urgent revascularization) after a minimum of 2 years follow-up. The SECURE trial is funded by the European Union Horizon 2020 Research Support Program and coordinated by the Centro Nacional de Investigaciones Cardiovasculares (CNIC) in Spain. SECURE will start enrolling patients soon in in seven EU countries: Spain, Italy, Germany, France, Poland, Hungry and Czech Republic.

Polypill as a cost effective strategy in cardiovascular prevention

Considering the rising healthcare costs and their impact on the economy, it is critical to understand what the future might hold for CVD prevalence and cost. Currently, CVD is the leading cause of death and in the United States it already constitutes 17% of overall national health expenditures. Projections show that between 2010 and 2030, real total direct medical costs of CVD are projected to triple, from $272.5 billion to 818.1 billion [5] (Figure 1). Part of the huge economic burden of CVD falls on the limited effectiveness of pharmaceutical treatment due to non-adherence to medication. In fact, direct and indirect costs of non-adherence to chronic treatments have been calculated between $100billion and $289billion annually in the US [41,42]. Non-adherence leads up to €1.25 billion in annually within the European Union with poor adherence to CVD medication accounting for 9% of all European CVD events [43]. Therefore, efforts to promote adherence are gathering worldwide attention from patients, providers, payers and regulators. A variety of interventions have been proposed, and range from blister packaging, case management, education with behavioral support, reminder calls, pharmacist-led, multicomponent interventions, education with behavioral support, collaborative care, shared decision making. Not all interventions, however, provided evidence of benefit [44]. Complex interventions are generally believed to be more effective that simple ones, however little is known about potential trade-off between their increased costs and the cost saving that might be reduced from increased adherence. Moreover, complex interventions that may show effectiveness in a high income settings are generally non applicable to limited resource settings, where the burden of CVD is highest. For this reason, there has been a tremendous effect in analyzing the potential cost effectiveness of a CV polypill in various resource settings.

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. [26] 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 results of a Markov-model-based cost-effectiveness analysis of the use of a polypill in the UK for secondary CVD prevention from improved adherence, have been recently published [27]. The model compared the use of Trinomia (Fuster-CNIC-Ferrer polypill brand name containing 100 mg aspirin, 20 mg atorvastatin and 2.5, 5, or 10 mg ramipril) with multiple monotherapy. Outcome measures were CV events prevented per 1000 patients; cost per life-year gained; and cost per quality-adjusted life-year (QALY) gained. The model estimates that for each 10% increase in adherence, an additional 6.7% fatal and non-fatal CV events can be prevented. In the base case, over 10 years, the polypill would improve adherence by ~20% and thereby prevent 47 of 323 (15%) fatal and non-fatal CV events per 1000 patients compared with multiple monotherapy, with an incremental cost-effectiveness ratio (ICER) of £8200 per QALY gained. Probabilistic sensitivity analyses for the base-case assumptions showed an 81.5% chance of the polypill being cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained compared with multiple monotherapy. In scenario analyses that varied structural assumptions, ICERs ranged between cost saving and £21,430 per QALY gained. Based on this model, the polypill appears to be a cost-effective strategy to prevent fatal and non-fatal CV events in the UK. Furthermore, assuming that some 450,000 adults are at risk of MI, a 10 percentage point uptake of the polypill could prevent 3260 CV events and 590 CV deaths over a decade [27].

Conclusions

The concept of a polypill, composed of a combination of medications that are known to effectively treat CVD, has been proposed as a simple, cost effective and innovative public health strategy to combat the CVD epidemic on a global scale. Several studies have shown the polypill to be well tolerated and superior in terms of adherence to standard of care.
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 CV clinical trials, such as FREEDOM, BARI-2D, and COURAGE have demonstrated that current treatment strategies for secondary prevention are not effectively improving the risk profiles of patients with CVD [45]. Also, large epidemiological studies have shown CVD therapy to vary across socioeconomic levels with the worst outcomes in LMICs [12]. Polypills have emerged as a way to bridge this treatment gap through simplifying treatment algorithms, improving patient adherence, improving accessibility, and reducing CV events and associated 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). This has led to regulatory approval of the Fuster-CNIC-Sincronium® CV Polypill in more than 20 countries to date and its commercialization in 8 countries in Mexico, Central America, South America and Europe under the brands of Trinomia® and Sincronium®.

The results of various trials under way (SECURE, TIPS-3, and HOPE-4) designed to show actual reductions in morbimortality (e.g., in LMICs [12]. Polypills have emerged as a way to bridge this treatment gap through simplifying treatment algorithms, improving patient adherence, improving accessibility, and reducing CV events and associated 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). This has led to regulatory approval of the Fuster-CNIC-Sincronium® CV Polypill in more than 20 countries to date and its commercialization in 8 countries in Mexico, Central America, South America and Europe under the brands of Trinomia® and Sincronium®.

The results of various trials under way (SECURE, TIPS-3, and HOPE-4) designed to show actual reductions in morbimortality will provide the ultimate evidence for the global implementation of this cardiovascular prevention strategy.

Conflict of Interest Statement

Drs. Fuster, Castellano and Bueno are PI, co-PI and scientific coordinator, respectively, of the SECURE trial. No other conflicts of interest to report.

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