A polypill strategy for global secondary cardiovascular prevention: a worldwide reality

Guest Editor
Valentín Fuster

Editor-in-Chief
Andrew J.S. Coats
A polypill strategy for global secondary cardiovascular prevention: a worldwide reality

Guest Editor: Valentín Fuster

This supplement has been sponsored by Ferrer

Available online at www.sciencedirect.com
A polypill strategy for global secondary cardiovascular prevention: a worldwide reality

Global burden of CVD: focus on secondary prevention of cardiovascular disease
Sameer Bansilal, José M. Castellano, Valentín Fuster

The cardiovascular polypill: clinical data and ongoing studies
José M. Castellano, Héctor Bueno, Valentín Fuster

The Fuster-CNIC-Ferrer Cardiovascular Polypill: a polypill for secondary cardiovascular prevention
Juan Tamargo, José M. Castellano, Valentín Fuster
Global burden of CVD: focus on secondary prevention of cardiovascular disease

Sameer Bansilab, José M. Castellanoab,c, Valentín Fustera,b,*

* Corresponding author at: Mount Sinai Heart, One Gustave L. Levy Place, Box 1030 New York City, NY 10029. Tel.: +1212.241.3852; fax: +1212.423.9488. E-mail address: valentin.fuster@mountsinai.org (V. Fuster).

Abstract

Despite encouraging advances in prevention and treatment of atherothrombosis, cardiovascular disease (CVD) remains a major cause of deaths and disability worldwide and will continue to grow mainly due to the increase in incidence in low and middle income countries (LMIC). In Europe and the United States of America (USA), coronary heart disease (CHD) mortality rates have decreased since the mid-1990s due to improvements in acute care, however the prevalence of CHD is increasing largely in part due to the overall aging of the population, increased prevalence of cardiovascular (CV) risk factors, and improved survival of patients after a CV event. Data from clinical trials has consistently proven the efficacy of pharmacologic interventions with aspirin, statins, and blood pressure (BP)-lowering agents in reducing the risk of CV events and total mortality in the ever growing pool of patients in secondary prevention. However, large gaps between indicated therapy and prescribed medication can be observed worldwide, with very low rates of use of effective therapies in LMIC countries. Adherence to medication is very poor in chronic patients, especially those treated with multiple pharmacologic agents, and has been directly correlated to a greater incidence of recurrent CV events and increase in direct and indirect healthcare costs. In this article, we review the global burden of CV disease, status of secondary prevention therapy and major barriers for treatment adherence.

© 2015 Elsevier Ireland Ltd. All rights reserved.

The global cardiovascular disease pandemic, current status and future projections

Despite encouraging advances in our knowledge of the prevention, diagnosis and treatment of atherothrombosis, cardiovascular disease (CVD) remains a major cause of disability and premature death throughout the world [1]. Globally an estimated 16.7 million deaths in the year 2010 were attributed to CVD; with projections showing a staggering 23.3 million by 2030. CVD mortality rates are considered equivalent to the combined number of deaths due to nutritional deficiencies, infectious diseases, and maternal and perinatal conditions [2]. This massive growth of CVD during the last decade is mainly due to the increasing incidence in low-and middle-income countries (LMICs) [2]. In 2012, the Developed and Caucasus and Central Asia regions had the highest CVD death rates in the world (>400 deaths per 100,000 population, in both genders). Lowest CVD death rates were estimated for the Oceania region (85 deaths per 100,000 population, in both genders) [3] (Fig. 1).

CVDs (including coronary heart disease (CHD), stroke and other CVD) cause more than 4 million deaths each year in the 53 countries of the World Health Organization (WHO) European Region and over 1.9 million deaths in the European Union (EU) countries [4]. Data from the Organisation for Economic Co-operation and Development (OECD) show that in 2010, coronary heart disease (CHD) alone was responsible for 13% of all deaths in EU member states. However, mortality from CHD varies considerably being generally higher in the countries of the former communist bloc. Rates are also relatively high in Finland and Malta, being several times higher than in France, Portugal, the Netherlands and Spain. Rates are generally lower in the southern countries, frequently considered to be a consequence of the Mediterranean diet. In all countries, death rates for CHD are higher for men than women in 2012 [4] (Fig. 2).

Since the mid-1990s, CHD mortality rates have declined in most European countries. Declining tobacco consumption contributed significantly to reducing mortality rates but improvements in medical care have also played a part. A recent study compared short-term outcomes in patients with acute myocardial infarction (MI) in the United Kingdom (UK) and Sweden. Unadjusted 30-day mortality was more than a third higher in the UK (10.5% [95% CI: 10.4–10.6]) than in Sweden (7.6% [95% CI: 7.4–7.7]) in 2004–2010. The authors suggest that the difference is mostly due to the more rapid adoption of new technologies and recommendations for practice in Sweden than in the UK despite similar spending on acute MI in both countries [5]. In the United States of America (USA), CHD alone caused 375,295 deaths. Each year an estimated 635,000 Americans have a new coronary attack (defined as first hospitalized MI or CHD death) [6].
Several studies in Europe have demonstrated that due to stabilisation of the incidence of MI and the case-fatality decrease, the prevalence of CHD is increasing. Recurrent CVD events are common in people who have already had a MI. Various studies have found a recurrence rate of close to 50% for any CVD event [7,8] or for subsequent revascularisation [9] in the year after an MI, and up to 75% of patients have a recurrent event within 3 years [8,10] (Fig. 3). A recent report from Denmark showed increasing prevalence of CHD associated with a decline in mortality and ageing of the population. The number of prevalent cases of CHD in Denmark increased from 125,000 in 2000 to 150,000 in 2009 and the number of people having survived an acute MI increased from 67,000 to 72,000. This study showed that about 3% of the Danish population has CHD [11]. A recent study sought to characterise the incidence for first and recurrent acute MI in England in 2010 by means of a population based national-linked database study. Overall, the annual age-standardised event rate of all acute MI (first and recurrent) per 100,000 was 174 (95% CI: 173–176) in men and 73.7 (95% CI: 72.9–74.5) in women. Of all the events that occurred: 83% were first acute MIs and 13% were re-infarctions. One-third (32%) of all acute MIs were fatal, with about two-thirds of deaths being sudden acute MI deaths. Similar proportions of all events were first and recurrent acute MI deaths (23% and 21%, respectively) [12]. In the USA, an estimated 300,000 have a recurrent attack [6]. In addition, 17.1% of acute MI were followed by a readmission within 30 days in 2009. For 1.6% of the index admissions the reason for readmission was a new MI, while for 2.0% the reason was a scheduled revascularization, for 2.3% it was heart failure or shock and the remaining 11.2% of index admissions were readmitted for other conditions and procedures [10].

As short-term survival in acute MI hospitalised patients improves, it becomes more important to understand the implications for longer-term prognosis, both with respect to survival and the risk of recurrence [13]. Factors associated with higher risk of recurrence include: older age, socioeconomic status, no revascularization procedures, presence of co-
morbidities, and lack of adherence to secondary prevention medication [12]. Both clinical care and secondary prevention are important in improving the long-term outcome of hospitalized patients with acute MI.

**Current status of secondary prevention, accessibility and adherence to cardiovascular drugs**

According to a WHO report, effective reduction of CV mortality should be based on three key points: surveillance (mapping and monitoring the epidemic of CVDs), prevention (reducing exposure to risk factors) and management (equitable health care for people with CVD) [14] (Fig. 4).

Overwhelming data from clinical trials show that pharmacologic interventions with aspirin, statins, and BP (BP)-lowering agents considerably reduce the risk of vascular events and total mortality [15–17]. Current European Cardiovascular Prevention Guidelines in patients with established coronary artery disease recommend the use of antiplatelet therapy, lipid-lowering agents when low-density lipoprotein (LDL) cholesterol ≥2.5 mmol/L, a beta-blocker, and additional BP-lowering agents in the case of a systolic BP ≥140 mm Hg, unless contraindicated [18,19]. The American Heart Association and the American College of Cardiology Foundation (AHA/ACC) Guidelines promote the standard use of cholesterol-and BP-lowering agents, regardless of the initial levels of LDL cholesterol or BP in patients with established vascular disease [20,21].

In clinical practice, a substantial proportion of CHD patients should be treated with aspirin, a statin, and BP-lowering agents as a result of tailored and/or step-up therapy. However, large gaps between indicated therapy and prescribed medication can be observed worldwide, with very low rates of use of effective therapies in LMICs countries [22,23]. In the secondary prevention setting in high-income countries, around 60% of patients are prescribed anti-platelet therapy, 50% beta-blockers, 40% angiotensin converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) and almost 70% statins [23]. An analysis of data from the Antiplatelet Treatment Observational Registry (APTOR) in 14 European countries showed that only 43% of patients who had an acute coronary syndrome (ACS) event between 2007–2009 were receiving optimal secondary prevention (defined as use of aspirin and clopidogrel as well as three or more of the following post-discharge medications: statins, beta-blockers, ARB/ACEI, exercise or diet) at baseline and 1-year post-discharge. There was considerable variation by country in prescription of optimal therapy with highest rates reported for Austria/Hungary and lowest rates for the Czech Republic [24] (Fig. 5). The results of a prospective epidemiological registry conducted in Europe showed that the overall use of combination therapy with aspirin, statin, and ≥1 BP-lowering agent increased substantially from 9% in 1996 to 66% in 2009. Except for CHD, the trend to use combination therapy addressed to different risk factors increases very slowly and that means that there are still a high proportion of high risk patients not achieving a complete protection [25]. In the USA, Muntner et al. estimated that among patients with a history of CV disease, only 44.5% received aspirin, 87.8% received antihypertensive medication, and 64.6% received statins [26]. The WHO study on Prevention of Recurrences of Myocardial Infarction and StrokE (WHO-PREMISE) study found that in some LMICs fewer than 40% of acute MI patients received ACEIs, and only 20% received statins [27]. The Prospective Urban Rural Epidemiological (PURE) study of individuals from rural and urban communities in countries at various stages of economic development aged 35–70 years confirmed that adherence with drugs for secondary prevention in patients with CVD was generally low and worst in the low income countries; with over 80% receiving none of the effective drug treatments in South Asia [23].

Another fact that might affect the therapy of patients with CVD is the accessibility to medication, which is highly different among the different regions and countries of the world. In the EU, although there are differences between countries in relationship to healthcare systems the availability of drugs is very high compared to the LMICs. Cameron et al. assessed the availability of a basket of 15 medicines in the public and private sectors of 36 LMICs. Overall, generic medicines were not adequately available in both the public and private sectors (median availability of 38% and 64%, respectively) [29]. An analysis performed by Commonwealth Fund survey revealed that in the USA, particularly the relatively young and healthy, are more likely to use prescription drugs than are the residents of Australia, Canada, Germany, the Netherlands, New Zealand, and the UK, but they also experience more financial barriers in accessing medications and spend more out-of-pocket for prescriptions. In the USA, there are also larger income-related inequities in pharmaceutical use [28].

**Low adherence: prevalence, causes and burden of disease of non-adherence**

On the other hand, adherence to prescribed medication – the extent to which patients take their medications as prescribed –
is generally poor for all diseases but especially poor for chronic conditions requiring long-term drug treatment such as CVD [29,30]. A systematic review of studies in adherence among patients with CVD showed that overall adherence was 57% over a median of 24 months [31]. In a systematic review and meta-analysis of 44 unique prospective studies (cohort, nested case–control, or clinical trial) comprising 1,978,919 non-overlapping participants at high CV risk, showed that 60% of included participants had good adherence (adherence ≥80%) to CV medications [32].

WHO has categorized potential barriers for medication non-adherence into five groups, including patient, condition, treatment, socioeconomic, and health system related factors [33,34]. The most common barriers for medication non-adherence have been the focus of numerous investigations of adherence [35,36]. The cross-sectional Phase 1 of the FOCUS (Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention) study showed that 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 [37]. The concern about medication side effects and patient’s lack of confidence in the benefit of treatment all play a role in the lack of adherence. Poor provider-patient relationship and difficulties accessing physicians or pharmacies are, among other, relevant socioeconomic factors [38]. Chowdhry et al. conducted a retrospective study in a cohort of lower income post-MI retired patients in the USA. Results showed that only 38.6% of patients receiving a statin after discharge were fully adherent [39]. Finally, Akincigil et al. examined the duration of CV treatment within 24 months after a MI. 7% of patients receiving ACEI prescription discontinued treatment within 1 month, 22% at 6 months, 32% at 1 year and 50% at 2 years [40]. Finally, suboptimal medication adherence is associated with racial/ethnic minority groups. Ens et al. literature review examining factors contributing non-adherence to CV medications in South Asian’s (India and Pakistan) showed that medication side-effects, cost, forgetfulness and higher frequency of dosing contributed to non-adherence. South Asian immigrants also faced language barriers, which contributed to non-adherence [41].

Many studies have evaluated the effect of adherence with prescribed medications on outcomes in patients with existing CVD who need secondary prevention therapy [42–44]. These studies show that good adherence (generally defined as >80% adherence) to the combined therapy with aspirin, ACEI, beta-blockers and statins is associated with improved outcomes (reduction in CV events, all-cause mortality or CVD mortality, and reduced medical or pharmacy costs) [42–44]. So, in the previously cited systematic review and meta-analysis conducted by Chowdhry et al. of participants at high CV risk (≥18 years old), risk estimates of CVD (defined as any fatal or non-fatal CHD, stroke or sudden cardiac death) and/or all-cause mortality (defined as mortality from any cause) outcomes were reported. Overall, 60% (95% CI: 52–68%) of included participants had good adherence (adherence ≥80%) to CV medications. The relative risk reduction (RRR) of any CV disease in the adherent patients was of a 20% when compared to patients with poor adherence (RR 0.80 [95% CI: 0.77–0.84]) Corresponding RRR in all-cause mortality was of a 38% in good vs. poor adherers (RR 0.62 [95% CI: 0.57–0.67]). These associations remained consistent across subgroups representing different study characteristics. According to these results, a considerable proportion of all CVD events (approximately a 9% in Europe) could be attributed to poor adherence to vascular medications alone [32]. In the USA, Newby et al analyzed the use of evidence based therapies during the period from 1995 to 2002 for patients with documented CHD in the Duke Databank for Cardiovascular Disease. They showed that consistent use of CV medication in patients with CHD was associated with statistically significant lower adjusted mortality [45].

The burden of acute coronary syndromes (ACS) to healthcare services in five European countries (UK, France, Germany, Italy and Spain) was determined including medications prescribed, intervention rates and hospital utilisation as well as health outcomes during the first year following a diagnosis of ACS. All costs were reported in 2004 Euros. Overall, the major contributors to total costs were hospital stay and revascularisation procedures. The total cost of ACS was estimated to be €1.9 billion in the UK, €1.3 billion in France, €3.3 billion in Germany, €3.1 billion in Italy and €1.0 billion in Spain. The cost per ACS patient ranged from €7,009 in the UK to €12,086 in Italy [46]. The results of a systematic review studying the impact of medication adherence on CHD costs and outcomes found that the annual cost of treating an adherent compared to a non-adherent patient was significantly different ($4,040 versus $4,940 respectively, p<0.01) [47]. A systematic review concluded that the overall costs of care are lower in patients who are adherent to secondary prevention, although medication costs are higher in adherent patients than those who do not take their prescribed medications [47]. Finally, out-of-pocket payments for the treatment of CV diseases lead to significant costs for households in LMICs. Up to 71% of patients who had an acute stroke were found to face catastrophic health expenditure in China, and 37% of them fell below the poverty line (1 USD per day) after paying for healthcare bills [48]. This evidence shows the potential of strategies that increase adherence to cut direct healthcare costs.

Strategies to improve adherence to medications: an integrated approach

Different disease specific, patient, provider and health system barriers have already been identified as key players to be addressed in order to increase adherence across populations [38,49]. Measures to enhance adherence to help maximize the potentials of effective cardiac therapies in the clinical setting are urgently required. This is reflected in the ESC Cardiovascular prevention Guidelines, where adherence assessment in secondary prevention is a Class 1A recommendation stating that physicians must assess adherence to medication, and identify reasons for non-adherence in order to tailor further interventions to fulfill the individual needs of the patient or person at risk [19].
Patient-targeted strategies

Strategies to address therapy-related barriers to medication adherence in patients with CV disease have primarily focused on reducing the complexity of the prescribed medical regimen. Polypharmacy is a potentially modifiable and important component of adherence to medical therapy for patients with chronic conditions. Different ad-hoc tools such as electronic medication aid caps have been developed to be delivered directly to the patient to enhance use of CV medications as prescribed. In addition, technology-based strategies such as cutting edge-technology in pill bottles which communicate with a health-coach [50] are being studied at this time. As a matter of fact, the Randomized Evaluation to Measure Improvements in Non-adherence from Low-Cost Devices (REMIND) trial is currently evaluating the impact on medication adherence of three different pill-box devices [51]. Data showing the efficiency of these approaches is still lacking. Another novel strategy that attempts to address the adherence issue is the use of a CV polypill as evidence suggests that reducing dosage demands is the most effective single approach to enhancing medication adherence [19]. Including the key medications necessary to reduce CV risk into a single, once daily dose pill improves treatment adherence, and could reduce CV events, hospitalizations and therefore lower costs [52,53]. The Heart Outcomes Prevention Evaluation (HOPE-4) trial [34] and the Secondary prevention of CardiovasCULAR disease in the Elderly (SECURE) trial are large CV outcomes-based randomized controlled trials testing the polypill concept.

Provider-targeted strategies

Strategies aimed at improving patient’s knowledge towards CV disease and use of medication as prescribed have increasingly focused on the role of highly labor intensive multidisciplinary care teams. These programs involve, between others, strategies such as individual counseling, medication education, pharmacy post-discharge programs and visiting nurse or nurse-practitioner based services. Berben et al. evaluated which strategies CV nurses and allied health professional utilize to enhance medication adherence. Results showed that educational interventions were the most frequently used tools. As a matter of fact, participants reported using a higher proportion of educational/cognitive interventions (36%) than counseling/behavioral (32%) or psychological/effective interventions (23%). Reading materials about CV care was the most used adherence-enhancing specific intervention, with 66% of respondents using it frequently. Only half of the participants (48%) reported that they frequently trained patients on how to properly take their medications as prescribed during their inpatient recovery [54]. Nieuwkerk et al. examined the effect of nurse-led counseling program regarding CV risk on adherence to statins. Patients taking statins for either primary or secondary prevention of CV disease were randomized to routine care or to the intervention arm. The intervention consisted of nurse-led individualized counseling regarding CV risk and subsequent regular visits to assess the degree of control of dyslipidemia and other CV risk factors. At the completion of the trial, self-reported adherence to statins was significantly higher in the intervention arm as compared to those who received routine care (100% vs. 95%; p<0.05) [55]. The addition of a clinical pharmacist to monitor patients with CVD can lead to an improvement in CVD patients in many areas, including patient improvement of adherence medications and preventing potential drug-related problems. Hohmann et al. evaluated the adherence to hospital discharge medication in patients with ischemic stroke before and after implementing a program provided by a clinical pharmacist. In the intervention group, the clinical pharmacist listed the medication at discharge and gave detailed information for all medication changes during hospital stay. Significant differences between the control group and intervention group were established with regard to adherence to both antithrombotic medications (83.8% control group vs. 91.9% intervention group, p=0.033) and to statin therapy (69.8% control group vs. 87.7% intervention group; p<0.001) [56]. None of these studies mentioned before reported economic outcomes.

Health system-targeted strategies

Medication non-adherence is increasingly recognized to be associated with socioeconomic adversity. Factors such as poverty and in particular food insufficiency and hunger [57], and unstable housing [58] have been associated with medication non-adherence in other chronic conditions such as human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS). In relation to CVD, low socioeconomic status has been found to be associated with low adherence in a number of different environments. Pharmacy benefit programs have a direct influence on adherence to medicines. Higher copays and restricted benefits lead to a reduction in use of medicines as prescribed. The Rand study performed in the USA found that doubling copays for commonly used drug classes reduced adherence by 25% to 45% [57].

Strategies may be more effective if they: 1) are designed for specific groups; 2) take into account behavioral patterns; and 3) are based on evidence-based specific tools or programs. Multifaced strategies simultaneously directed at patients, physicians/practices, and healthcare or social systems targeting physician prescribing behavior as well as interventions to reduce social, financial and treatment-related barriers to enable patients to adhere to prescribed therapy have been found to be most effective in low income groups. Moreover, complex multifactorial strategies, addressing different barriers have been mostly assessed without previous evaluation of their individual components [59]. Individual interventions such as simplifying dosage regimens and fixed combination pills appear to be the most effective tool. The European Guidelines on CVD prevention recommend all the physicians to reduce dosage demands of their patients to the lowest feasible level and additionally, to provide clear advice regarding the benefits and possible adverse effects of the medication as well as of the duration and timing of dosing. It is recommended to consider patients’ habits and preferences and to ask patients in a non-judgmental way how the medication works for them, discussing possible reasons for non-adherence (e.g. side effects, worries). After the assessment of adherence it is important to implement repetitive monitoring and feedback, offering multisession or combined behavioral interventions in the case of persistent non-adherence through physicians assistants and/or trained nurses [19].

Conclusion

It is clear that the current CVD pandemic calls for a revision of the way we implement healthcare worldwide, as well as new simple, efficacious and efficient strategies to contain the growth of the disease worldwide.

The scenario in LMIC is especially worrisome, as many regions suffer what has been called the double burden of disease (that is, developing regions where communicable diseases are highly prevalent are also suffering the health toll from chronic, non-communicable diseases). In high income countries the higher survival rate after a CV event, the aging of the population and the increase in prevalence of CV risk factors has increased the
cost of treating CVD to a degree that will not be sustainable even in the wealthiest economies. Even in high income European countries where medication accessibility is guaranteed the efficacy of proven treatments is severely hampered due to poor adherence rates to pharmacologic therapy (consistently shown to be about 45–60% in secondary prevention). Hence, interventions toward improving adherence rates could have a far greater impact on public health than any individual treatment. Barriers to medication adherence might be surpassed through programs delivered through the healthcare system, through multidisciplinary care teams or directly by the patient by reducing the dosage demands which could include the intake of CV polypills. Hence, from a public health perspective, it is of highest importance implement existing and innovative strategies to achieve adequate adherence to secondary CV prevention medication in order to ensure efficacy of treatment.

Conflict of Interest Statement

Nothing to declare.

References


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 have proposed a more selective use of polypills for primary prevention in individuals without 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
Table 1
Principal Clinical Trials using a CV Polypill

<table>
<thead>
<tr>
<th>Trial/Sample Size/Principal Investigator(s)</th>
<th>Population</th>
<th>Polypill Composition</th>
<th>Outcomes</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indian Polycap Study (TIPS) n=2053</td>
<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>Yusuf S, Pais P</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly-Iran: Phase II Study of Heart Polypill Safety and Efficacy in Primary Prevention of CV Disease n=475</td>
<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>Marshall T, Malekzadeh R, Malekzadeh F</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination Therapy Trial n=200</td>
<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>Furberg C, Mendis S, Soliman E.Z.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMProving Adherence using Combination Therapy (IMPACT) n=497</td>
<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-cholesterol at 12 months</td>
<td>Completed</td>
</tr>
<tr>
<td>Rodgers A, Selak A.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indian Polycap Trial (TIPS)-3 n=5000</td>
<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>Yusuf S, Pais P, Xavier D, Liu L.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Outcomes Prevention Evaluation (HOPE)-3 n=12,500</td>
<td>Primary prevention in men aged ≥55 years and women aged ≥65 years with at least 1 CV risk factor and with average BP and cholesterol levels in 22 countries</td>
<td>Rosuvastatin 10 mg, candesartan 16 mg, hydrochlorothiazide 12.5 mg (≥2 factorial design)</td>
<td>Major CVD events; neurocognitive function; renal function</td>
<td>Estimated study completion date: March 2016</td>
</tr>
<tr>
<td>Yusuf S, Lon L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOCUS Trial in Secondary Prevention Phase 1: n=2000, Phase 2: n=800</td>
<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>Fuster V</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of a Multidrug Pill In Reducing CV Events UMPIRE n=2000</td>
<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>Thom SA, Rodgers A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel n=623</td>
<td>Established CVD or high risk primary prevention (5-year CVD risk of &gt;15%)</td>
<td>Aspirin 75 mg, simvastatin 40 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>Use of a Multidrug Pill In Reducing CV Events UMPIRE n=2000</td>
<td>Established CVD or high-risk primary prevention (5-year CVD risk of &gt;15%) in Australia</td>
<td>Aspirin 75 mg, simvastatin 40 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>SECURE Trial n=3200</td>
<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>
<tr>
<td>Fuster V, Castellano JM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 (atenolol 50 mg, hydrochlorothiazide 12.5 mg, and ramipril 5 mg), 20 mg of simvastatin, and 100 mg of aspirin. In total, 518 individuals eligible for secondary prevention were randomly allocated to receive either a single polypill, or 2 capsules of the polypill plus K+ 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 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 rosvuastatin 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 CV 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 pharmacological treatment due to non-adherence to medication. In fact, direct and indirect costs of non-adherence to chronic treatments have been calculated between $100 billion and $289 billion 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-Ferrer 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 Sincromium®.

The results of various trials under way (SECURE, TIPS-3, and HOPE-4) designed to show actual reductions in morbidity 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.

**References**


The Fuster-CNIC-Ferrer Cardiovascular Polypill: a polypill for secondary cardiovascular prevention

Juan Tamargo\textsuperscript{a}, José M. Castellano\textsuperscript{b,c}, Valentín Fuster\textsuperscript{b,d,*}

\textsuperscript{a} Department of Pharmacology, School of Medicine, Universidad Complutense, 28040, Madrid, Spain
\textsuperscript{b} Centro Nacional de Investigaciones Cardiovasculares (CNIC) Carlos III, Madrid, Spain
\textsuperscript{c} HN Hospitals, Hospital Universitario Montepríncipe, Madrid, Spain
\textsuperscript{d} Mount Sinai Cardiovascular Institute, New York, USA

\textbf{KEYWORDS}

Trinomia\textsuperscript{e}, Sincronium\textsuperscript{e}, Iltria\textsuperscript{e} cardiovascular polypill, Ramipril, Atorvastatin, Simvastatin, Aspirin, Secondary prevention

\textbf{ABSTRACT}

During the last decade, there has been a tremendous effort to develop different cardiovascular polypills in response to the upsurge in global cardiovascular disease worldwide. The pharmacological development of such a strategy has proven to be extremely complex from a formulation standpoint. Not all drugs are suitable for use in a polypill because of potential drug incompatibilities between them. Candidate agents must be safe, well tolerated, effective, guideline recommended and physicochemically compatible with the other components of the pill.

The Fuster-CNIC-Ferrer cardiovascular (CV) polypill has been found to be the first-in-class polypill to be approved and commercialized in Europe and Latinamerican Countries. In this article, we review the pharmacological properties of its three components, including the clinical evidence supporting their use in patients with established cardiovascular disease, their pharmacokinetic properties, adverse effects, drug interactions and contraindications.

\textcopyright{} 2015 Elsevier Ireland Ltd. All rights reserved.

1. The Fuster-CNIC-Ferrer CV Polypill: making the leap from conceptual debate to worldwide reality

Moving from the theoretical proposal of a CV polypill 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 \cite{1}. Although the idea of combining so many compounds into a single pill may seem attractive for some patient populations, the reality is that the difficulty of manufacturing a combination pill increases with each component due to challenges related to the chemical properties of each substrate (Figure 1). The concept of a CV polypill for secondary prevention proposed by Fuster et al. resulted from having a clear picture of the global burden of cardiovascular disease (CVD) \cite{2}. The effectiveness of the drugs included in a polypill are generally well understood, and the principles behind using pharmacotherapy at a population level are that the drugs themselves should have a well-known risk/benefit ratio and should be supported by an evidence-based efficacy and safety in secondary CV prevention. On the other hand, a polypill is simple to administer and is an effective option to increase adherence in order to reduce CV events on top of the promotion of lifestyle changes for multiple risk factor control \cite{3}.

The Fuster-CNIC-Ferrer CV polypill (commercialized under Trinomia\textsuperscript{e}, Sincronium\textsuperscript{e} and Iltria\textsuperscript{e} brand names) was developed within a very clear conceptual framework: to provide accessibility of treatment to as many patients worldwide for the longest periods of time so as to prevent recurrence of events and death, by simplifying treatment in a cost effective way \cite{2,4}. At the core of this concept lies the decision of including guideline recommended therapy for secondary prevention, namely, blood pressure control and prevention of the LV remodeling process that accompanies cardiac dysfunction after myocardial infarction (MI), cholesterol lowering, plaque stabilization and use of antiplatelet drugs to prevent further CVD events, all of which are known to be effective in secondary prevention \cite{5,6}. From a clinical standpoint, each additional drug presents the possibility for more adverse effects (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 antithrombotic agent, a statin and blood pressure lowering agents (an angiotensin-converting enzyme (ACE) inhibitor and beta-blocker (BB) over a calcium channel blocker (CCB)) given the known mortality benefit of the former medications in post-MI patients. The Fuster-CNIC-Ferrer CV polypill does not include...
a BB in their combination pill, based on clinical and technical aspects. Clinically, beta-blockers appropriately titrated are indicated in patients with STEMI, NSTEMI, and LV dysfunction with or without signs of heart failure [7,8]. In stable coronary heart disease (CHD), there is solid evidence to show that BB effectively relieve anginal symptoms and improve myocardial ischemia, and are therefore recommended as first-line agents for symptom relief in both U.S. [9] and European [10] guidelines. However, the evidence base for the use of BB to improve prognosis in asymptomatic patients, who represent about 80% of the stable CHD population [11], is less robust and not supported by data from an appropriately powered randomized trial [12]. Additionally, a recent report from the REACH registry has demonstrated that BB usage in patients with stable CHD was not associated with a reduced rate of CV death, nonfatal MI, nonfatal stroke, hospitalization for an atherothrombotic event, or revascularization, even in patients with previous MI [13]. While guidelines currently recommend 3 years of BB treatment after presentation with acute coronary syndrome (ACS) [9], should side effects occur there is no definitive evidence to insist on continued treatment citing concerns about needing to increase the number of formulations of the pill to allow for dose adjustments in order to limit side effects.

The concern about limiting the number of formulations of the combination pill is well founded because from a technical standpoint there is an almost linear relationship between the number of active components in the polypill and the difficulty of formulation (Figure 1). 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 ASA at 100 mg) causes technical problems with the analytical methods used in purification and bioanalytics. The formulation of a combination polypill also has illustrated the potential for drug incompatibilities and issues with bioavailability.

Fig. 1. Relationship between the number of drugs in a polypill and the formulation challenges, patentability, and clinical value. Adapted from Guglietta A. and Guerrero M. (reprinted with permission, license number: 3640791509009).

The Fuster-CNIC-Ferrer CV Polypill has been developed by a technologic platform patented by Ferrer. The combination of different active ingredients in a single capsule has been achieved avoiding the physico-chemical incompatibilities conserving at the same time the biopharmaceutical and pharmacokinetic properties of every one of its components (Figure 2).

The combination of atorvastatin, ramipril and acetylsalicylic acid (ASA) shows a clear chemical incompatibility between the three active ingredients. The employed technology achieves the stabilization of all of them inside one single pharmaceutical form, a capsule.

At the same time, some of the components show a very high pharmacokinetic variability which difficults enormously the bioequivalence achievement. The Fuster-CNIC-Ferrer CV polypill technology has allowed the administration of a single pharmaceutical form to be equivalent to the concomitant use of every one of the single active ingredient individually administered.

The Fuster-CNIC-Ferrer CV polypill includes ASA (100 mg), ramipril (in doses of 2.5, 5, or 10 mg) and Atorvastatin 20 mg.

2. Pharmacological characteristics of Trinomia®

Extensive controlled, randomised studies have demonstrated that treatment with the proposed dosages of ASA, atorvastatin, and ramipril decrease mortality in patients with established CVD [14–16]. There is also extensive experience with the combination therapy of these medications in free combinations for CV prevention, with an adequate risk/benefit ratio, in clinical practice.

2.1. In vitro and in vivo studies with Trinomia®

2.1.1 In vitro: biopharmaceutical studies

A battery of comparative in vitro dissolution studies between the biobatch for the fixed-dose combination (test) and the reference products for ASA (Aspirine N® 100mg), Ramipril 10mg (Acoval®), and atorvastatin (Cardyl® 20 mg) used in the bioequivalence studies, found that there is a similar in vitro dissolution profile between the biobatch and the reference products used in the bioequivalence study [17].

2.1.2 In vivo: biopharmaceutical studies: bioequivalence study

Ferrer Internacional, S.A. (Barcelona, Spain) performed a randomised, open-label, two-period, two-sequence, controlled, cross-over, bioequivalence study of single-dose atorvastatin 20 mg, ramipril 10 mg, and ASA 100 mg fixed-dose combination capsule vs. equivalent doses of Cardyl® 20 mg film-coated tablets + Acoval® 10 mg tablets + Aspirin N® 100 mg tablets (reference formulations), in order to establish the rate and extent of absorption of Trinomia® compared to the individual components. The study was carried out under fasting conditions (bioequivalence studies in fasting conditions are considered...
Table 1
Results of bioequivalence studies comparing components of the Fuster-CNIC-Ferrer CV Polypill to monocomponents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parameter</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>96.92–104.47</td>
<td>BE</td>
</tr>
<tr>
<td>Cmax</td>
<td>84.51–95.78</td>
<td>BE</td>
</tr>
<tr>
<td>Ramipril</td>
<td>108.13–120.11</td>
<td>BE</td>
</tr>
<tr>
<td>Cmax</td>
<td>91.51–112.62</td>
<td>BE</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>95.50–105.93</td>
<td>BE</td>
</tr>
<tr>
<td>Cmax</td>
<td>94.58–116.14</td>
<td>BE</td>
</tr>
</tbody>
</table>

The upper and lower CL (confidence level) demonstrate that the ratio and corresponding 90% confidence interval of the relative AUC0–t and Cmax were within the pre-specified 80.00 to 125.00% bioequivalence range for all components of the fixed combination. AUC0–t, area under the curve; Cmax, maximum plasma concentration; CI, confidence interval; BE, bioequivalence.

to be the most sensitive condition to detect a potential difference between formulations. Even though there are no relevant interactions with food for any of the components, it is recommended to take the Fuster-CNIC–Ferrer CV polypill after meals in order to improve tolerability mainly related to aspirin. In accordance with the Guideline on the Investigation of Bioequivalence [18], this study confirms the bioequivalence of Trinomia as the geometric 90% confidence intervals for the log-transformed results of the area under the plasma concentration-time curve from time 0 to the last sampling time [AUC0–t] and peak plasma concentrations (Cmax) within the acceptable interval of 80% to 125% for aspirin, atorvastatin, and ramipril (Table 1). Thus, the Fuster-CNIC–Ferrer CV polypill is the first-in-class polypill that has been found bioequivalent as compared with the individual components of the polypill.

Regarding safety, the results of this bioequivalence study also confirmed that there is no difference in tolerance and safety between the two treatment groups.

2.2. Pharmacodynamic properties of the components of Trinomia®

Long-term, controlled, randomised studies have demonstrated that treatment with the dosages of ASA, atorvastatin, and ramipril contained in the Fuster-CNIC–Ferrer CV polypill decrease mortality in patients with established CVD. There is also extensive experience with the combination therapy of these medications in free combinations for CV prevention, with an adequate risk/benefit ratio, in clinical practice [10].

2.2.1. Ramipril

This angiotensin converting enzyme inhibitor (ACEI) decreases plasma and tissular levels of angiotensin II (Figure 3A) [19]. The maximum inhibition of plasma ACE activity (>90%) appeared within 1–4 hours and persisted inhibited by 80% after 24 hours. Epidemiological studies have consistently demonstrated that high blood pressure levels correlate with the risk of CVD and cerebrovascular accidents [20] and antihypertensive drugs reduce the risk of both conditions, not only in hypertensive patients, but also in those who have a high CV risk and normal blood pressure. Present ESC guidelines recommend ACEIs in hypertensives with LV hypertrophy, HF or LV dysfunction, myocardial infarction (MI), diabetes, peripheral artery disease, chronic kidney disease or microalbuminuria, metabolic syndrome and atherosclerosis [21]. The Heart Outcomes Prevention Evaluation (HOPE) trials showed that in high risk patients ≥55 years of age with evidence of CVD or diabetes plus a CV risk factor ramipril (10 mg/day over 5 years) significantly reduced the rates of death, MI, and cerebrovascular accidents [22]. A similar benefit was reproduced in diabetic patients. In this study, ramipril also significantly reduced the development of HF in patients without known low LV ejection fraction or HF and in elderly patients reduced the risk of major CV events, CV deaths, MI, and cerebrovascular accidents.

A meta-analysis of the HOPE, the European trial on Reduction Of cardiac events with Perindopril among patients with stable coronary Artery disease (EUROPA), and the Prevention of Events with ACE inhibition (PEACE) trials found that ACEIs significantly reduce serious vascular events in patients with atherosclerosis without known evidence of HF or LV systolic dysfunction [23]. Similarly, ACEIs reduce total mortality and major CV end points in patients who have CHD and no LV systolic dysfunction or HF [24]. In patients with MI the Acute Infarction Ramipril Efficacy (AIRE) Study [15] showed that ramipril produces a 27% risk reduction (RR) in mortality compared with placebo. This benefit persisted in patients taking aspirin. Interestingly, ACEIs were effective when administered with antiplatelet and lipid-lowering agents. In the Ramipril Efficacy in Nephropathy (REIN) trial ramipril reduced the glomerular filtration rate decline more than expected from the blood pressure drop [25]. Therefore, present AHA/ACC and ESC guidelines recommend ACEIs for all patients with an EF ≤40% to reduce the risk of HF hospitalization and the risk of premature death [6,9] and in all patients after an ACS in the absence of contraindications [10].

2.2.2. Atorvastatin

This selective and competitive inhibitor of the (3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase reduces the hepatic synthesis of cholesterol (Figure 3B). In patients with hypercholesterolemia or with mixed hyperlipidemia, atorvastatin dose-dependently (10–80 mg daily) decreases total cholesterol (30–46%), LDL-C (37–55%), apolipoprotein B (34–50%) and triglycerides (14–33%) plasma levels, and produces variable increases in HDL-C (2–12%) [26].

Statins are effective in the primary prevention and secondary prevention of CV diseases [27]. In a meta-analysis of 27 trials (n=174,149), a 1 mmol/L (40 mg/dL) reduction in LDL-C levels by statin therapy results in a 21% RR in major vascular events (MI, coronary death, coronary revascularization, or stroke) and a 12% RR in vascular mortality [28]. In the GReek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study, long-term treatment of CHD with atorvastatin (mean dose 24 mg/day) significantly reduced the relative risk, in comparison to usual care, of all-cause (RRR 43%), coronary mortality (RRR 47%) and morbidity (RRR 54%) and stroke (RRR 47%) [14]. In a cohort study, statin therapy produced a 40% RRR in hospitalisation for acute MI; the 20 mg daily of atorvastatin was equipotent to 80 mg of pravastatin, 160 mg of fluvastatin, and 40 mg of simvastatin [29]. Furthermore, early atorvastatin therapy (20 mg/day within 48 hours) reduced long-term major adverse cardiac and cerebrovascular events (MACCE) as compared with placebo. (30) A review of 52 clinical studies recommended 20 mg of atorvastatin as the standard initial dose in patients requiring a LDL-C reduction of 35–50% [31]. In the NICE Guideline 2014 Lipid modification [32] a daily 20 mg dose of atorvastatin reduces LDL-C to a similar extent (43%) than 10 mg of rosuvastatin and 80 mg of simvastatin, and more than 40 mg of pravastatin and 40 mg of simvastatin. This guideline recommends atorvastatin 20 mg for the primary prevention of CVD to people with or without type 2 diabetes who have a 10% or greater 10-year risk of developing CVD, for the secondary prevention of CVD to people with chronic kidney disease (CKD) and for people ≥85 years to reduce the risk of non-fatal MI. Because 20 mg atorvastatin dose presents a good overall balance between efficacy and safety, this dose was selected for Trinomia®.
2.2.3. Aspirin

Aspirin inhibits platelet aggregation by irreversibly inhibiting the enzyme cyclooxygenase-1 (Figure 3C) and its antiplatelet effect lasts for the duration of platelet life (~10 days) [33]. In randomised, controlled trials in patients with one or more major CV risk factors or who have suffered a MI have demonstrated the efficacy of low-doses of aspirin in the prevention of CV deaths and total cerebrovascular accidents [34]. Interestingly, the efficacy of low doses of aspirin (up to 325 mg/day) in preventing the risk of MI or stroke is greater than with higher doses. A meta-analysis of 287 randomised trials confirmed that long-term treatment with aspirin (75–125 mg/day) for secondary prevention in a wide range of patients with high CV risk (patients with a history of MI, stroke or transient ischemic attacks, or some major CV events) achieved a RRR of 32% in the incidence of new cardiovascular events, with no apparent adverse effect on non-cardiovascular deaths whereas the RRR for the same outcomes was a 26% for the dose range from 160–325 mg and only of 19% with doses ranging from 500 mg to 1500 mg [35]. Because of its favorable benefit-risk ratio, lifelong low-doses of aspirin (75–125 mg) are the cornerstone for the secondary prevention of MI and death in patients with coronary artery disease and other atherosclerotic cardiovascular disease unless contraindicated [6,9,36].

The Fuster-CNIC-Ferrer CV polypill contains 100 mg of ASA, dose included in the most favourable recommended dosage range by the current prevention guidelines [6].

2.3. Pharmacokinetic properties of the components of Fuster-CNIC-Ferrer CV Polypill (Table 2)

2.3.1. Ramipril

It is rapidly absorbed, reaching peak plasma concentrations (C_max) within 1 h. The rate, but not the extent, of absorption is delayed with food (19) Ramipril is almost completely biotransformed in the gut wall and the liver into its metabolite ramiprilat, which has about 6 times the ACE inhibitory activity of ramipril and reaches its C_max within 2–4 h and steady-state plasma levels after 4 days. The C_max and the 24-hour AUC for ramiprilat are linear at doses of ramipril between 2.5 and 10 mg [37]. Ramipril and ramiprilat bind to plasma proteins and are widely distributed, reaching higher concentrations in kidneys and lungs than in blood [37]. Ramipril and its metabolites are excreted in urine (60%, but <2% as unchanged ramipril) and faeces. After multiple daily doses of 5 and 10 mg of ramipril, the half-life of ramiprilat is 13–17 hours. ACEIs can cause fetal and neonatal morbidity and death when given to pregnant women (Pregnancy Category D). There is no information on the use of ramipril during breastfeeding.

2.3.2. Atorvastatin

It is rapidly orally absorbed, but presents low oral bioavailability due to high pre-systemic clearance. Food can decrease the rate and extent of drug absorption, but does not modify the reduction
on LDL-C. Atorvastatin highly binds to plasma proteins and presents a large volume of distribution; thus, hemodialysis does not increase drug clearance [38]. Atorvastatin is a substrate of the hepatic uptake transporter OATP1B1 and is predominantly metabolised by cytochrome P450 3A4 (CYP3A4) into metabolites that are responsible for 70% of its LDL-C lowering effects, undergo further metabolism via glucuronidation and are eliminated in bile. The \( C_{\text{max}} \) and AUC of atorvastatin are 4- and 11-fold greater in patients with Childs-Pugh A and B disease, respectively. Thus, Fuster-CNIC-Ferrer CV Polypill® is contraindicated in patients with severe liver failure. Conversely, since <2% of the dose is excreted in urine, dose adjustment are not necessary in patients with mild-moderate CKD [39]. The half-life of atorvastatin is ~14 hours, but the half-life of the inhibitory activity for HMG-CoA reductase is 20–30 hours due to its active metabolites. This explains why LDL-C reduction is the same regardless the time the drug is administered. Atorvastatin use is contraindicated in pregnancy (Pregnancy Category X), but it is unknown whether the drug or its metabolites are excreted in human breast milk [19].

2.3.3. Aspirin

It is rapidly and almost completely absorbed in the stomach and small intestine [41], reaches the \( C_{\text{max}} \) within 15–20 minutes and platelet function is inhibited within 1 hour. Aspirin is rapidly biotransformed by plasma and tissular esterases into salicylic acid being undetectable 1–2 h after dosing (half-life ~15–20 min). Salicylic acid reaches the \( C_{\text{max}} \) within 1–2 h, binds to plasma proteins (90–99%) and is widely distributed to all tissues, crosses the blood-brain barrier and the placenta and is excreted into breast milk. At low doses (<250 mg), salicylic acid is glucoconjugated in the liver with glycin (salycilureic acid) and to a lesser extent with glucuronic acid and presents an elimination half-life of 2–4 hours [60]. Salicylic acid is excreted mainly in urine, but its urinary excretion increases 10–20 times (from 5% to more than 80%) when urine pH rises from 5 to 8 [42]. Pregnant women (Pregnancy Category D) and those breastfeeding should avoid taking aspirin unless specifically advised by their doctor.

2.4. Safety of the components of Fuster-CNIC-Ferrer CV Polypill

Acetylsalicylic acid, atorvastatin, and ramipril have been marketed at the proposed dosages worldwide for decades, with an established safety profile, and are available as generic products. This extensive, long-term use of the three drugs in clinical practice provides a large patient population for analysing the safety of these three drugs. On the other hand, the dosage regimen proposed for this polypill (once per day) is the same as for all of the active components. Therefore, it is not expected that changing from the concurrent use of the three individual pills in free combination to the polypill will result in a potentially different safety profile.

2.4.1. Ramipril

Adverse effects are mild and transient, and drug discontinuation due to AEs effects is observed in 3% of patients. The most common AEs include hypotension, dry cough, dizziness, headache, asthenia, nausea and gastrointestinal (GI) disturbances [43]. Other AEs include a decrease in hemoglobin or hematocrit, dermatological reactions (rash, urticaria, pruritus, photosensitivity), neurologic reactions (headaches, blurred vision) and impotence. Because ramipril decreases aldosterone release, hyperkalemia can occur, particularly in patients with renal failure.

Hypotension can be observed at the beginning of the treatment, particularly in patients with HF post-MI, renal artery stenosis, hyponatremia, hypovolemic or increased serum creatinine (1.5–3 mg/dL or 135–265 mol/L). Ramipril produces a preferential vasodilatation of glomerular efferent arterioles, reduces the intraglomerular pressure and may increase serum creatine levels at the beginning of treatment in patients with hypotension, hyponatremia or renal insufficiency and in hypertensive patients with unilateral or bilateral renal artery stenosis. ACEIs can produce angioedema, particularly in blacks; warning signs include facial swelling, unilateral facial or periorbital oedema [44].

2.4.2. Atorvastatin

The most frequently described AEs are GI (anorexia, nausea, flatulence, and constipation), headache, skin rashes, dizziness, blurred vision, insomnia, and dysgeusia [45]. Myopathy, characterised by myalgia and muscle weakness with increased levels of creatine phosphokinase (CPK) >10 times the upper limit of normal (ULN) has been reported, especially in patients treated potent CYP3A4 inhibitors, cyclosporine, fbrates or niacin (Table S1) [46,47]. Rhabdomyolysis is a very rare AE (~1 per 100,000 patient-years); if suspected or diagnosed,
at orvastatin should be discontinued immediately. Transaminase elevations >3 times ULN occurs in 0.2%, 0.2%, 0.6% of patients treated with atorvastatin 10, 20 and 40 mg, but serious liver injury rarely occurs. Other reported AEs include amnesia, increased weight, nightmares, paresthesia, peripheral edema and thrombocytopenia. New-onset diabetes has been reported, but the risk is low both in absolute terms and when compared with the reduction in coronary events [48]. Treatment with statins for 4 years resulted in 1 extra case of diabetes, whereas 5.4 coronary events (coronary death, non-fatal MI) are prevented [49]. In postmarketing studies, rare and reversible AEs, including hepatitis, pancreatitis, depression, bullous rashes and hypersensitivity reactions, have been reported.

2.4.3. Aspirin

The most common AEs are GI (dyspepsia, nausea, and diarrhea). (46) These AEs are usually mild, although in patients a peptic ulcer severe GI hemorrhage may occur [50]. Aspirin increases major (hemorrhagic stroke) and minor bleeding (epistaxis, hematuria, melena, bruising), but when used in secondary prevention, the balance clearly favors benefit. In a meta-analysis, aspirin (75–325 mg/day) increased the risk of major GI bleeding and intracranial bleeding versus placebo [51], but 769 patients (95% CI 500–1250) need to be treated to cause 1 additional major bleeding episode annually. The risk of GI bleeding increases when aspirin is co-administered with other NSAIDs, antiaggregants or anticoagulants [52]. In patients at increased risk of GI bleeding, a proton pump inhibitor should be used.

Others adverse effects include weakness, dizziness, tinnitus, edema, hyperkalemia and deterioration of renal function. Allergic responses (anaphylactic shock, skin rash, asthma) are rare (<0.5%), but aspirin may precipitate bronchospasm in patients with asthma or NSAID-precipitated bronchospasm. Aspirin has been implicated in some cases of Reye syndrome, so it should not be prescribed in children and adolescents under 18 years of age.

In recent decades, there has been concurrent use worldwide of the three drugs for secondary prevention of CVD as a free combination, which has provided solid evidence on the appropriate risk/benefit ratio. This drug combination has not been associated with an increased incidence of adverse effects.

The conclusions of the fixed-dose combination safety study carried out by Yusuf et al. with Polycap with five components, although carried out in primary prevention, confirmed that the safety of the fixed-dose combination was similar to treatment with each drug in monotherapy. The study found there were no increases in adverse events specific to the drug [53].

The recent published FOCUS study with a polypill containing aspirin, simvastatin and ramipril compared to the monocompounds in 695 post MI patients also confirmed that there were no differences in the occurrence of adverse events between both groups whereas the polypill treated group showed a significantly greater adherence rate compared to the control group after 9 months of follow up [4].

2.5. Drug Interactions

The main drug interactions of ramipril, atorvastatin and aspirin are summarized in Additional file 1 (Table S1). A potential interaction between ACEIs and aspirin was proposed as aspirin inhibits prostaglandin synthesis and causes sodium and water retention which might potentially counteract the blood pressure lowering effects of ramipril. However, the evidence of this potential interaction came from clinical trials not designed to examine this issue [54]. Indeed, several studies and two meta-analysis confirmed the efficacy and safety of ACEIs in patients treated with aspirin [55,56]. A meta-analysis of 6 long-term trials (22,060 patients) found that ACEIs significantly reduced the risk of the major clinical outcomes, both among in patients receiving (OR 0.80, 99% CI 0.73–0.88) or not aspirin at baseline (0.71, 99% CI 0.62–0.81) [57]. In 96,712 patients allocated to receive ACEIs or standard therapy in the acute phase of MI (0–36 h from onset), ACEI therapy was associated with similar reductions in 30-day mortality, irrespective of whether or not aspirin was given [58]. Furthermore, in patients with CAD and diagnosis of HF, the use of aspirin in conjunction with ACEIs does not worsen long-term survival compared to the use of ACEIs without aspirin [55]. Thus, there is no evidence of a decreased efficacy of ACEIs when coadministered with low doses of aspirin (up to 200 mg).

Interestingly, a synergy between statins and ACEIs has been suggested [59]. In a post hoc analysis of the GREEK Atorvastatin and Coronary-heart-disease Evaluation (GREACE) trial in high-risk patients with CAD treatment with statins and ACEIs significantly reduced the cardiovascular events (all-cause and coronary mortality, nonfatal MI and stroke) more than statins alone and considerably more than ACEIs alone [60]. Moreover, in the HOPE trial the benefit of ramipril was observed in patients already treated with aspirin, beta-blockers, and statins [22].

2.6. Posology

The Fuster-CNIC-Ferrer CV Polypill should be administered once daily, preferably after food and accompanied by liquid to reduce the risk of GI effects caused by the aspirin. The capsules should not be opened, chewed, or crushed. For the prevention of CV events, the recommended maintenance dose of ramipril is 10 mg daily. In elderly patients, treatment should be initiated with precaution due to the higher risk of adverse effects. In patients with CKD the daily dose of Fuster-CNIC-Ferrer CV Polypill should be based on creatinine clearance (crCl). When the crCl is ≥60 mL/min, the maximum daily dose of ramipril is 10 mg, if crCl is 30-60 mL/min the maximum daily dose of ramipril is 5 mg, but the Fuster-CNIC-Ferrer CV Polypills contraindicated in patients in hemodialysis or with severe kidney failure (CrCl <30 mL/min) (Table 3) [16]. Liver function tests should be carried out in patients with liver disease before beginning treatment with the Fuster-CNIC-Ferrer CV Polypill and periodically afterwards. Patients who developed increased levels of transaminases should be monitored until the abnormality is resolved and the Fuster-CNIC-Ferrer CV Polypill should be discontinued if the increase in transaminase is >3× the ULN. The maximum daily dose of ramipril in this patient group is 2.5 mg.

2.7. Contraindications

The main contraindications of the Fuster-CNIC-Ferrer CV Polypill are a compilation of the ones described in the summary of product characteristics of each of the single components and are summarized in Table 3. The Fuster-CNIC-Ferrer CV Polypill is therefore contraindicated in women who are pregnant, trying to become pregnant, or suspected to be pregnant because it can produce teratogenic effects [19]. It should also be avoided during lactation as small amounts of statins and aspirin are found in the mother’s milk and is contraindicated in children and adolescents under 18 years of age [16].

3. Fuster-CNIC-Ferrer CV polypill marketing authorization

The Fuster-CNIC-Ferrer CV Polypill (Trinomia®, Sincronium®, Iltria®,) including aspirin (100 mg), ramipril (in doses of 2.5, 5, or 10 mg to allow for titration) and atorvastatin 20 mg has been
Table 3

Contraindications of the Fuster-CNIC-Ferrer CV Polypill [13]

- Hypersensitivity to the active substances, to any of the excipients, to other salicylates, to NSAIDs, to any other ACE inhibitor, or to tartrazine
- Hypersensitivity to soya or peanut
- History of previous asthma attacks or other allergic reactions to salicylic acid and other NSAIDs
- Acute gastric and enteric ulcers
- Hemophilia and other clotting disorders
- Severe or active liver disease, or unexplained persistent elevations of serum transaminases ≥3× ULN
- Severe kidney failure (creatinine >221 mmol/L or eGFR <30 mL/min/1.73 m²) or haemodialysis
- Severe heart failure
- Concomitant treatment with methotrexate at a dosage ≥15 mg per week
- Patients with nasal polyps associated to asthma induced or exacerbated by aspirin
- During pregnancy, lactation and in women of child-bearing potential not using appropriate contraceptive measures
- Concomitant treatment with tipranavir, ritonavir or cyclosporine due to the risk of rhabdomyolysis
- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or ARBs).
- Extracorporeal treatments which involve blood contact with negatively charged surfaces
- Bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney
- Ramipril should not be administered to hypotensive or hemodynamically unstable patients.
- Children and adolescents below 18 years of age during episodes of fever-causing or viral illness

Approved at present by the Medicine Agencies of 15 European countries (Austria, Belgium, Bulgaria, Czech Republic, Finland, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Rumania, Spain, Sweden) and Chile for its use in secondary prevention of CV events. The indication for its use is for the secondary prevention of CV events as substitution therapy in adult patients adequately controlled with the monocomponents given concomitantly at equivalent therapeutic dosages [13]. Currently it has been marketed in Spain, Portugal, Romania and Germany under two different brand names: Trinomia® and Sincronium®.

During the next years, it has been planned to launch the Fuster-CNIC-Ferrer CV polypill in additional European countries as well as worldwide.

4. Conclusions

The concept of a pill containing guideline recommended therapy for secondary prevention, composed of aspirin, an antihypertensive agent and a statin has been suggested for over a decade to simplify treatment complexity, increase accessibility to treatment and serve as a cost effective public health strategy to improve pharmacological treatment worldwide. In stark contrast to the simple concept of the cardiovascular polypill itself (including three active principles in one pill) the pharmacological development of such a strategy has proven to be extremely complex from a formulation point of view. The Fuster-CNIC-Ferrer CV Polypill has made the leap from this conceptual debate to clinical reality and has become first in class to achieve bioequivalence of all components, which in turn has led to widespread approval by regulatory agencies.

Additional file

Additional file 1: Table S1 Drug interactions of the components of the Fuster-CNIC-Ferrer CV Polypill (Trinomia®, Sincronium®, Iltria®).

Financial disclosure

The authors have no financial disclosures or relationships to report.

Conflict of Interest Statement

No conflict of interest to report.

References

<table>
<thead>
<tr>
<th>Interacting drug(s)</th>
<th>PD/PK consequence</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ramipril</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Antihypertensives</td>
<td>Increase the antihypertensive response of ramipril</td>
<td>Monitor blood pressure</td>
</tr>
<tr>
<td>• Vasodilators (e.g. nitrates)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Anesthetic agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Antipsychotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tricyclic antidepressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARBs, Beta-blockers, Heparin, K+-sparring diuretics, K+ supplements, Tacrolimus, Trimethoprim.</td>
<td>Increase the risk of hyperkalemia</td>
<td>Monitor plasma potassium levels</td>
</tr>
<tr>
<td>Cyclosporine, NSAIDs, Vasopressor sympathomimetics</td>
<td>Inhibit the antihypertensive response of ramipril</td>
<td>Monitor blood pressure</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>May produce renal failure in the elderly or dehydrated patients</td>
<td></td>
</tr>
<tr>
<td>Lithium salts</td>
<td>Decreases lithium renal excretion and increases plasma levels and toxicity.</td>
<td>Monitor lithium plasma levels</td>
</tr>
<tr>
<td>Oral antidiabetic agents or insulin</td>
<td>Increase the risk of hypoglycaemia</td>
<td>Monitor glucose plasma levels</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Higher doses of erythropoietin are needed in dialysed patients</td>
<td></td>
</tr>
<tr>
<td>Aliskiren, ARBs</td>
<td>Increased renal dysfunction</td>
<td>Avoid the combination</td>
</tr>
<tr>
<td>Drugs eliminated by the kidney:</td>
<td>Ramipril decreases their renal clearance</td>
<td>Monitor drug response</td>
</tr>
<tr>
<td>• Atenolol, Flecainide, Disopyramide, Nadolol, Procalmainamide, Sotalol, Temsirolimus</td>
<td>Increased risk for angioedema</td>
<td>With caution</td>
</tr>
<tr>
<td><strong>Atorvastatin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong CYP3A4 inhibitors:</td>
<td>Significantly increased the Cmax of atorvastatin and the risk of myopathy</td>
<td>Atorvastatin should be used with caution and close clinical monitoring is recommended.</td>
</tr>
<tr>
<td>• Azole antifungals (Itraconazole, Ketoconazole, Posaconazole, Voriconazole), Clarithromycin, Telithromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• HIV-protease inhibitors: Atazanavir, Darunavir, Fosamprenavir, Indinavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hepatitis C protease inhibitors: telaprevir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Other: Ciclosporin, Delavirdine, Stiripentol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate CYP3A4 inhibitors:</td>
<td>They may increase the Cmax of atorvastatin and the risk of myopathy.</td>
<td>Starting dose: 10 mg/day</td>
</tr>
<tr>
<td>• Amiodarone, Erythromycin, Fluconazole, Fluoxetine, Grapefruit juice, Lomipatide, Verapamil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe, Fibrates, Fusidic acid, Gemfibrozil, Niacin</td>
<td>Increased risk of myopathy and rhabdomyolysis</td>
<td>Avoid combination with gemfibrozil. Clinical monitoring is recommended</td>
</tr>
<tr>
<td>CYP3A4 inducers:</td>
<td>It increases the Cmax of atorvastatin</td>
<td>Variable decrease in the plasma concentrations of atorvastatin</td>
</tr>
<tr>
<td>• Carbamazepin, Eferivenz, Rifampin, St. John’s wort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OATP1B1 inhibitors: Cyclosporine</td>
<td>Plasma digoxin levels increase (20%)</td>
<td>Monitor digoxin plasma levels</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Cases of myopathy and rhabdomyolysis, have been reported</td>
<td>Caution when prescribing atorvastatin with colchicine.</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Increased AUC values for norethindrone and ethinyl estradiol</td>
<td>Select the proper oralanticonceptive</td>
</tr>
<tr>
<td><strong>Aspirin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Alcohol</td>
<td>The risk of GI ulcers and bleeding increases</td>
<td>Monitor for signs of external or internal bleeding</td>
</tr>
<tr>
<td>• Other antiaggregants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Anticoagulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Systemic glucocorticoids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Other NSAIDs/antirheumatics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Platelet antiaggregants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Selective serotonin and serotonin-norepinephrine reuptake inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tositumomab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEIs, ARBs, beta-blockers, thiazides</td>
<td>Aspirin can decrease their antihypertensive effects</td>
<td>Monitor blood pressure</td>
</tr>
<tr>
<td>Antiacids</td>
<td>Increase the renal excretion of aspirin</td>
<td>Monitor drug response</td>
</tr>
<tr>
<td>COX-1 inhibitors: (ibuprofen, naproxen)</td>
<td>Can prevent the antiaggregant and cardioprotective effects of aspirin</td>
<td>Avoid the combination</td>
</tr>
<tr>
<td>Ciclosporine</td>
<td>NSAIDs may increase the nephrotoxicity of ciclosporine</td>
<td>Careful monitoring of renal function</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Plasma digoxin levels increase (20%)</td>
<td>Monitor digoxin plasma levels</td>
</tr>
<tr>
<td>Diuretics</td>
<td>NSAIDs can cause acute renal failure in dehydrated patients</td>
<td>Monitor hydration of the patient</td>
</tr>
<tr>
<td>Methotrexate, tacrolimus</td>
<td>Aspirin displace these drugs from plasma proteins and decrease their renal excretion</td>
<td>Dose adjustment or more frequent monitoring of renal function and hemogram</td>
</tr>
<tr>
<td>Oral antidiabetic agents or insulin</td>
<td>Increase the risk of hypoglycaemia</td>
<td>Monitor glucose plasma levels</td>
</tr>
<tr>
<td>Urac acid</td>
<td>Aspirin inhibits kidneys’ ability to excrete uric acid and reduce the effect of uricosuric drugs</td>
<td>With caution in patients with hyperuricemia, or gout</td>
</tr>
<tr>
<td>Barbiturates, Lithium salts, Phenytoin, Zidovudine</td>
<td>Aspirin increases their plasma levels. It decreases the renal excretion of lithium</td>
<td>Monitor the patient’s response. Monitor plasma lithium levels</td>
</tr>
</tbody>
</table>

Scope
The International Journal of Cardiology is a world journal of clinical cardiology. Articles relating to clinical cardiology and cardiovascular medicine in its widest sense are welcome. Articles relating purely to experimental or theoretical topics may be considered, but authors will need to convince the editors of their clinical relevance. The journal aims to present all aspects of cardiovascular medicine of relevance to the clinical from genes to populations.

Preference for publication will be given to articles reporting original observations or research. The journal commissions high quality review articles from distinguished authors; unsolicited reviews which pass the peer review process will also be accepted. Letters to the editor are welcome. Case reports can only be considered in the form of research letters.

Editor-in-Chief
Professor Andrew J.S. Coats, The University of Sydney, NSW 2006 Australia, e-mail: ajscoats@aol.com

Editorial Manager
Dr. Louise Shewan, e-mail: internationaljournalcardiology@gmail.com

Associate Editors
Stefan D. Anker (Metabolic Cardiology)
Yi-Jen Chen (Cell Pathways)
Carlo Di Mario (Interventional Cardiology)
Rob Doughty (Cardioendocrinology)
Gerasimos S. Filippatos (Acute Cardiology)
Darrel P. Francis (Mathematical and Computing)
Abdel J. Fuenmayor (Electrophysiology and Arrhythmias)
Nobusada Funabashi (Imaging)
Michael A. Gatzoulis (Congenital Heart Disease)
Finn Gustafsson (Transplant and Devices)
Stephan von Haehling (Biomarkers)
Michael Y. Henein (Echocardiography)
Johan Herlitz (Epidemiology)
Liviu C. Hool (Cardiac Myocytes)
Martin St. John Sutton (Functional Imaging)
Anthony Keech (Clinical Trials)
IJaz A. Khan (Clinical Cardiology)
Kwang Kon Koh (Coronary Artery Disease)
Mitja Lainscak (Heart and Lung)

International Consulting Editor for China:
Tsung O. Cheng

International Consulting Editor for Japan:
Chuichi Kawai

Editorial Board
Enrico Agabiti-Rosei (Brescia, Italy)
Joseph S. Alpert (Tucson, USA)
Jeroen J. Bax (Leiden, The Netherlands)
Bradford Berk (Rochester, USA)
Luciano Bernardi (Pavia, Italy)
Mike Bristow (Denver, USA)
Morris Brown (Cambridge, UK)
Isabel Coma-Canella (Pamplona, Spain)
John Deanfield (London, UK)
Kenneth Dickstein (Stavanger, Norway)
Rainer Dietz (Berlin, Germany)
Gary S. Francis (Cleveland, USA)
Yoichi Goto (Osaka, Japan)
Masayasu Hiraoka (Tokyo, Japan)
Masatsugu Hori (Osaka, Japan)
Kevin Jennings (Aberdeen, UK)
Itsuo Kodama (Nagoya, Japan)
Michel Komajda (Paris, France)
Gregory Lip (Birmingham, UK)
Giuseppe Mancia (Monza, Italy)

Instructions to authors: The instructions can be found on the World Wide Web: access under http://www.elsevier.com/locate/ijcard

All manuscripts should be submitted online: http://ees.elsevier.com/ijc