

# Clinical Impact of the Polypill for Cardiovascular Prevention in Latin America

## A Consensus Statement of the Inter-American Society of Cardiology



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### ABSTRACT

The burden of cardiovascular diseases (CVD) is increasing, particularly in low-middle-income countries such as most of Latin America. This region presents specific socioeconomic characteristics, generating a high incidence of CVD despite efforts to control the problem. A consensus statement has been developed by Inter-American Society of Cardiology with the aim of answering some important questions related to CVD in this region and the role of the polypill in cardiovascular (CV) prevention as an intervention to address these issues. A multidisciplinary team composed of Latin American experts in the prevention of CVD was convened by the Inter-American Society of Cardiology and participated in the process and the formulation of statements. To characterize the prevailing situation in Latin American countries, we describe the most significant CV risk factors in the region. The barriers that impair the use of CV essential medications are also reviewed. The role of therapeutic adherence in CV prevention and how the polypill emerges as an effective strategy for optimizing adherence, accessibility, and affordability in the treatment of CVDs are discussed in detail. Clinical scenarios in which the polypill could represent an effective intervention in primary and secondary CV prevention are described. This initiative is expected to help professionals involved in the management of CVD and public health policymakers develop optimal strategies for the management of CVDs.

Cardiovascular diseases (CVDs) are responsible for 30% of global mortality and contribute substantially to increased health and economic costs in health care systems. It is estimated that by 2030, 23.3 million people could die from CVDs, mainly heart disease or strokes [1]. In the specific case of Latin America, CVD is the main cause of disability and death [2], accounting for 35% of all deaths and 68% of the total disease burden in this region [3].

CVD burden is related to socioeconomic level. A decline in the mortality rate of up to 60% was observed in developed countries such as the United States or Canada between 1970 and 2000, but in Latin America and the Caribbean, this decrease was less pronounced [4,5]. The most important reasons for this phenomenon include failure to control risk factors, lack of adherence to drugs and procedures of proved efficacy, and demographic transition [6,7]. The Pan American Health Organization adds that CV mortality rates in Latin America are very high because of the high prevalence of CV risk among the population [7].

Primary and secondary CV prevention in high-risk groups has historically focused on controlling modifiable

risk factors, such as hypertension, dyslipidemia, obesity, and diabetes, and on correcting unhealthy habits, especially those with the greatest impact: poor eating habits, sedentary lifestyle, smoking, and excessive alcohol consumption. However, the data suggest that a complementary approach to prevention is needed. In this respect, a significant proportion of morbidity and mortality could be prevented by implementing population strategies and accessible and affordable cost-effective interventions, both for CVD patients and for high-risk individuals [8]. Non-adherence to medication is a determining factor in the course of CVD [9], so a strategy that increases observance of clinical guidelines, fosters access, and improves adherence to medication could play a relevant role. These concepts led, more than 15 years ago, to the development of the CV polypill as a strategy to increase drug adherence and decrease CV morbidity and mortality [10,11].

Several polypills with different components now have marketing approval, and versions with and without acetyl salicylic acid (ASA) are available (Table 1) [12]. A polypill developed by Valentin Fuster and colleagues [13] for

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secondary prevention in the CV setting has recently been approved in more than 30 countries, including several in Latin America. This polypill contains 3 active principles with proven CV prevention benefits in a single capsule: ASA, ramipril, and a statin, which may be atorvastatin or simvastatin depending on the country where it is marketed. Polypill prescription is a strategy that promotes CV prevention by improving therapeutic adherence, accessibility, and affordability [13].

Against this backdrop, the purpose of this initiative of the Inter-American Society of Cardiology is to gather and present the evidence related to nonadherence as a public health problem in our countries and specifically address how polypill as intervention can help in Latin America to improve CV care, reducing the lack of adherence and improving CV risk factors' control.

#### DEVELOPMENT OF THE CONSENSUS STATEMENT

A multidisciplinary team composed of Latin American experts in the management and prevention of CVD was convened by the Inter-American Society of Cardiology and participated in the process and the formulation of statements. A coordinating committee of 2 experts was formed, along with a recommendation-formulating group that

included the coordinating committee, 7 more experts, and 2 consultants who provided advice throughout the entire process. A content index and a list of 24 relevant clinical questions (Online Appendix 1) were developed during the kickoff meeting. A nonsystematic expert search of the available publications related to these clinically relevant questions was conducted in September 2016 in appropriate databases such as PubMed, Scielo, Lilacs, and others, giving priority to those that were relevant to Latin America or conducted in Latin American countries. A total of 87 publications were retrieved. Question 9 required a non-exhaustive systematic publications review in PubMed performed on September 9, 2016, providing 6 publications (Online Appendix 2). At the discretion of the coordinating committee, 61 publications were included after reading the titles and abstracts of the manuscripts. After these publications were thoroughly examined, 58 were used by the recommendation-formulating group to prepare a document answering each clinical question that included potential statements and conclusions. Statements were debated during a structured in-person meeting. A total of 21 statements and conclusions were included. Statements that achieved unanimity (100% agreement) or consensus ( $\geq 80\%$  agreement) were accepted. Statements were formally categorized with their level of evidence and degree

**TABLE 1.** Available polypills with marketing approval

Polypill Contents (Marketing Name, Source)	Available Countries
Simvastatin, atenolol, thiazide, ramipril, and ASA (Polycap, Cadila)	India and Zambia
Atorvastatin or simvastatin, ramipril, and ASA (Trinomia, Ferrer)	Argentina, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Chile, Czech Republic, Dominican Republic, Ecuador, El Salvador, Finland, France, Germany, Greece, Guatemala, Honduras, Ireland, Italy, Kosovo, Macedonia, Mexico, Moldova, Nicaragua, Paraguay, Poland, Portugal, Romania, Serbia, Spain, Sweden, Ukraine, and Uzbekistan
Perindopril, amlodipine, and atorvastatin (Triveram, Servier)	Austria, Belgium, Bulgaria, Croatia, Czech Republic, Cyprus, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, and Slovenia
ASA, ramipril, and atorvastatin (Ramitorva, Zydus Cadila)	India
ASA, losartan, atenolol, and atorvastatin (Starpill, Cipla)	India
Atorvastatin, ramipril, and clopidogrel (Atamra CV kit, Amra)	India
Ramipril, metoprolol, atorvastatin, and ASA (CV-Pill kit, Torrent)	India
Ramipril, atorvastatin, and ASA (RIL-AA, East West Pharma)	India
Ramipril, metoprolol, atorvastatin, and ASA (ZYCAD-4 kit, Zydus Cadila)	India
Ramipril, atorvastatin, and ASA (Heart Pill, Excella Pharma)	India
ASA, atorvastatin, hydrochlorothiazide, and valsartan (Polypill-V, Alborz Darou)	Iran
ASA, atorvastatin, hydrochlorothiazide, and enalapril (Polypill-E, Alborz Darou)	Iran

ASA, acetyl salicylic acid; CV, cardiovascular; RILAA, ramipril, atorvastatin, and ASA; ZYCAD-4 kit, ramipril, metoprolol, atorvastatin, and ASA. Reproduced with permission from Webster et al. [12].

of recommendation, according to the SIGN (Scottish Intercollegiate Guidelines Network 1999–2012) [14]. A subsequent validation round was performed to increase the number and geographic distribution of experts. A Delphi-like process using an online questionnaire presented the validated statements to a group of 27 additional members representing 12 national cardiology societies belonging to the Inter American Society of Cardiology (37 were approached, representing a 73% of response rate).

## LATIN AMERICAN CV SCENARIO

### Cardiovascular disease risk factors in Latin America

In order to understand CVD in Latin America, it is important to determine the main CV risk factors in the region. Two large population-based case-control studies that included Latin American countries have been conducted to identify CV risk factors. The INTERHEART (Effect of Potentially Modifiable Risk Factors Associated With Myocardial Infarction) study [2,15] identified factors associated with acute myocardial infarction (AMI) in patients from Chile, Colombia, Brazil, and Argentina, and the INTERSTROKE (Risk Factors for Ischemic and Intracerebral Hemorrhagic Stroke in 22 Countries) study [16,17] identified factors associated with stroke in patients from Ecuador, Colombia, Argentina, Brazil, Chile, and Peru. The most important risk factors for AMI and stroke in Latin America, according to population-attributable risk and differentiated by sex, are shown in Table 2.

The CARMELA (Cardiovascular Risk Factor Multiple Evaluation in Latin America) study assessed the prevalence of CV risk factors and common carotid far wall intima-media thickness distributions in 11,550 individuals living in 7 Latin American cities (Barquisimeto, Venezuela; Bogota, Colombia; Buenos Aires, Argentina; Lima, Peru; Mexico City, Mexico; Quito, Ecuador; and Santiago, Chile) [18,19]. The prevalence of hypertension mirrored the world average in 3 cities but was lower in the rest. Hypercholesterolemia was highly prevalent even in countries of different socioeconomic levels. The prevalence of diabetes was similar to that in the developed countries. The rate of tobacco use in women living in Santiago and Buenos Aires was among the highest in the world. Intima-media thickness and carotid plaque prevalence varied widely among the participants in the CARMELA cities. On the basis of the Framingham risk score, 1 in 7 persons showed a significant risk for a CV event [18,19].

In the PURE (Prospective Urban Rural Epidemiology) study, although CVD risk factors were lower in low- and middle-income countries, the rate of major CV events (death due to AMI, stroke, or heart failure) was higher than those in high-income countries (5.38 and 6.43 events/1,000 in habitants/year vs. 3.99 events/1,000 inhabitants/year, respectively). The case fatality rate was also higher (15.9% and 17.3% vs. 6.5%). In line with these figures, the use of preventive drugs and revascularization procedures

**TABLE 2.** Population-attributable risk for AMI and stroke in men and women in Latin America

	Total (%)	Men (%)	Women (%)
<b>AMI</b>			
Abdominal obesity (WHR)	48.5	35.8	63.1
Altered ApoB/ApoA1	40.8	36	46.5
Smoking	38.4	42.5	25.7
Arterial hypertension	32.9	32	15.5
Permanent stress	28.1	32	15.5
Lack of exercise	28	28.1	27.9
Diabetes mellitus	12.9	9.8	22.6
Low consumption of fruit and vegetables	6.9	7.5	5.5
<b>Stroke</b>			
Arterial hypertension		45.2	52.3
Lack of exercise		37.3	32.4
Altered ApoB/ApoA1		25.1	29.2
Unhealthy diet		23.5	22.9
Psychosocial factors		18.5	15
Smoking		16.6	5.3
Abdominal obesity		12.7	25.8
Diabetes		3.7	4.1

AMI, acute myocardial infarction; ApoB/ApoA1, apolipoprotein B—apolipoprotein A1 ratio; WHR, waist-to-hip ratio.

was significantly lower in low- and middle-income countries [20].

### Barriers to cardiovascular drugs in Latin America

In order to reach the goal of a 25% reduction in early CV mortality by 2025, and as part of the World Health Organization (WHO) action plan 25 × 25, at least 50% of CVD patients must receive essential drugs for secondary prevention [21]. The current use rate and factors limiting use must then be determined. The PURE study showed that to offset these risk factors in Latin America, only 30.1% of CVD patients with a history of myocardial infarction were receiving ASA, 34.2% beta-blockers, 36% renin-angiotensin system blockers, and 18.0% statins; these rates were even lower among patients with previous stroke. A significant percentage of patients with previous myocardial infarction (31%) and stroke (54%) received no medication. Few patients received 3 (4.1%) or 4 (3.3%) drugs considered to be essential [22]. In high-income countries, the number of patients who did not receive any type of drug was 11.2%, compared with 45.1% in medium- to high-income countries, 69.3% in medium- to low-income countries, and 80.2% in low-income countries. National factors (e.g., the country's economic status) are more often associated with medication consumption rates than with personal factors (age, sex, education, smoking, body mass index, and diabetes) [22,23].

To explain these low treatment rates, it is necessary to understand that in low- and middle-income countries,

medicines account for 20% to 60% of health costs, compared with 18% in countries belonging to the Organisation for Economic Co-operation and Development [21]. On the other hand, up to 90% of the population in developing countries obtains drugs through direct payments. Specifically in the case of Latin America, an average of 78% of the whole cost of all medicines is paid out-of-pocket by the patient [24]. The high price of medicines can lead to treatment discontinuation or to family debt and, as a result, access to medicines is limited for a large part of the world's population. Medications also represent an important burden for government budgets [21], data corroborated by studies conducted in Latin America [25,26]. Similarly, it was observed that the number of individuals with previous CVDs (coronary heart disease or stroke) who had received treatment was higher in high-income countries than in low-income countries (antiplatelet agents: 62.0% vs. 8.8%; beta-blockers: 95% vs. 9.7%; angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers: 49.8% vs. 5.2%; statins: 49.5% vs. 3.3%, respectively), with lower treatment rates in countries with lower per capita income.

Another barrier to the use of CV medications is therapeutic inertia (TI). Several publications [27-29] drew attention to failures in decision making in the management of chronic disorders in asymptomatic phases, such as hypertension, dyslipidemia, and diabetes [30]. Failure to start, intensify, or modify treatment despite clinical guideline statements is now defined as TI [31]. Two types of TI have been determined: one occurring before treatment is initiated in the untreated, uncontrolled patient, and the other during treatment, in the patient who has received treatment but has not achieved control. The source of TI in terms of medical performance lies primarily in insufficient training, lack of knowledge, poor adherence to clinical guidelines, growing requirements for therapeutic targets, underutilization of available treatments, and overestimation of professional follow-up. Indeed, the medical act is a constant decision-making process, and to support this process, clinical guidelines based on scientific evidence are necessary. Table 3 depicts the conclusions and statements developed by the expert panel on CV risk factors and barriers to CV medication.

## ADHERENCE TO CARDIOVASCULAR MEDICATION

### Therapeutic adherence in cardiovascular prevention

WHO's adherence project has adopted the following definition of adherence to long-term therapy: "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [34]. Poor adherence to long-term therapies severely compromises the effectiveness of treatment, making this a critical issue in population health, both from the perspective of quality of life and of health economics.

Interventions aimed at improving adherence would provide a significant positive return on investment through primary prevention (of risk factors) and secondary prevention of adverse health outcome.

Lack of therapeutic adherence has negative effects on disease prognosis. It increases the risk of new CV events such as heart attack, stroke, and CV death and leads to significantly increases in health care costs [9]. In low- and middle-income countries, as in Latin America, adherence to medication is lower than in high-income countries [32]. Lack of adherence has been associated with an increase in long-term CV events, including AMI, stroke, CV mortality, and all-cause mortality [9,35]. In a meta-analysis conducted with data from the European Union, lack of adherence was identified as the cause of 13 CVD deaths per 100,000 inhabitants, and 9% of all CVD deaths were attributed to nonadherence. Conversely, good adherence is associated with a 20% lower risk of CVD and a 35% reduction in all-cause mortality [36]. In a study of patients who had experienced an AMI and received complete treatment (statins, beta-blockers, and ACE inhibitors), nonadherent patients did not benefit from the prescription of any of the 3 classes of drugs; moreover, adherent patients obtained a significant benefit in reducing new CV events [37]. In another study that included patients who had experienced an AMI or had atherosclerosis and were treated with statins and ACE inhibitors, AMI patients with full adherence had 27% fewer events than nonadherent patients did, and 19% fewer events than patients with partial adherence did. In patients with atherosclerosis, a 44% reduction in events was observed compared with those in nonadherent patients, and a 24% reduction compared with those in partially adherent patients [32].

### Factors that contribute to inadequate patient adherence to treatment

There is no single individual profile of a nonadherent patient, because the problem is multifactorial, and at least 4 dimensions influence adherence, all of which interact to a greater or lesser extent, depending on geographic region, the country's gross domestic product (GDP) and the health system characteristics [35,38]. These dimensions and their components are as follows [13,39,40]: (1) the patient dimension, comprising socioeconomic status, age, race, marital status, income, social support, health care coverage, educational level, knowledge of the disease, cognitive status, and depression; (2) the health care system, comprising availability, affordability, lack of incentives for health personnel, and saturation of the system; (3) the disease or condition, comprising chronicity, duration, absence of symptoms, and comorbidities; and (4) treatment, comprising polypharmacy, number of medications and pills, complexity of the therapeutic regimen, constant changes, and adverse effects. We can observe these dimensions depicted in Figure 1. In terms of economic costs,

**TABLE 3.** Statements and conclusions related to CVD risk factors and barriers to the use of CV drugs in Latin America

No.	Statement/Conclusion	LE/DR	CLA% (n)	DLA % (n)
1.	According to the results reviewed, the most modifiable risk factors for cardio-cerebrovascular disease in Latin America are hypertension, dyslipidemia, abdominal obesity, and smoking [2,15-17].	NA	100 (9)	96 (27)
2.	In our region, particularly in low-income countries, <10% of patients with CVD are receiving treatment with the 3 essential drugs that have proven useful in secondary prevention [32].	2++	100 (9)	93 (27)
3.	The GDP and the percentage of health spending in Latin American countries can be considered as potential barriers for the proper use of essential drugs in CV prevention [25].	2+/B	100 (9)	93 (27)
4.	In terms of availability, accessibility, and affordability, the following barriers to access should be taken into account: <ul style="list-style-type: none"> <li>• Lack of coverage and fragmentation of health systems.</li> <li>• High cost of drugs.</li> <li>• Cost of transportation and distance to the health center.</li> <li>• Economic status and educational level of the patient.</li> <li>• Lack of perception by the patient of the severity and importance of chronic diseases.</li> </ul> (Based on expert opinion.)	4/D	100 (9)	100 (27)
5.	Causes of lack of adherence should be identified from a clinical point of view, and strategies should be implemented to correct them [33].	2+/C	100 (9)	100 (27)

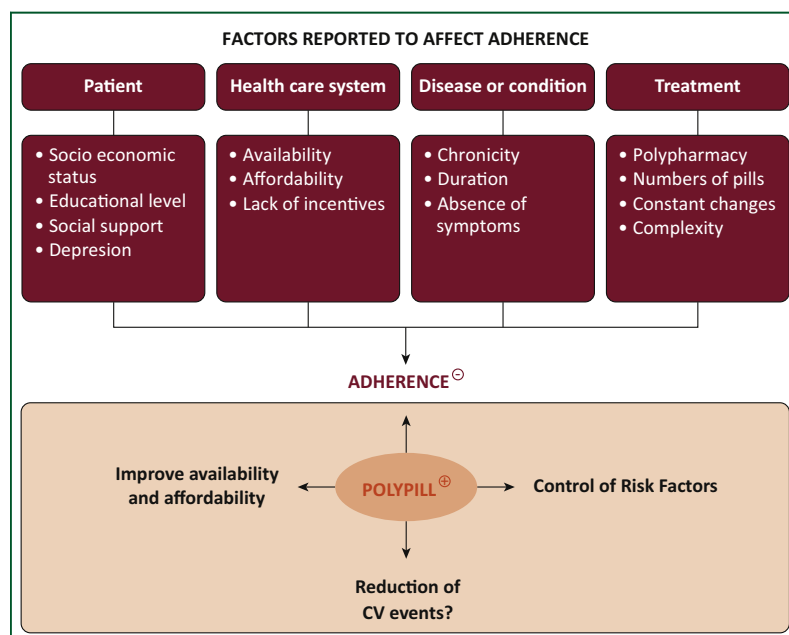
CLA%, percentage level of agreement in the total votes in the consensus meeting; CV, cardiovascular; CVD, cardiovascular disease; DLA%, percentage level of agreement in the total votes in the Delphi-like questionnaire; GDP, gross domestic product; LE/DR, level of evidence/degree of recommendation; NA, Not applicable.

lack of adherence is associated with a long-term increment of \$907/year/patient as calculated by Bansilal et al. [38].

At the health system level, although increasing drug use increases short-term costs, it leads in the long term to a decrease in the number of significant CV events and costs associated with hospitalization and treatment of the event. The net result is a reduction in health care costs. A systematic review found that adherence >80% is associated with a lower in expenditure of up to 18% [41]. A mathematical model applied to the economic consequences of the lack of adherence in chronic diseases showed that long-term adherence reduces costs of medical care by reducing hospitalizations and readmissions to the emergency room, despite the increased pharmaceutical expenditure [42].

### Strategies to improve adherence

The low adherence to prescribed CVD drugs and the impact on secondary prevention has prompted investigators to evaluate strategies for improvement. Such strategies can be implemented through the development of government health policies and interventions in routine clinical practice. These interventions can be classified according to their objective. Informational and educational interventions target the education of both the patient and their immediate contacts, while family and social support interventions aim to improve adherence by involving the patient's family or social environment. Interventions through group dynamics help increase patient



**FIGURE 1.** Barriers to access (red) to cardiovascular (CV) medication and solutions provided by the polypill (orange). In the following diagram, the main factors affecting adherence are represented in red, like those related to the health care system, patient, therapy, and finally those related to the disease condition. Polypill is depicted as a pivotal strategy to improve adherence, availability and affordability of medication, control of CV risk factors, and potentially improve the number of CV events.

motivation and follow-up. Behavioral reinforcement interventions can help improve patients' ability to manage their treatment, using accountability and self-management techniques.

Special proactive programs have been shown to be particularly useful in different clinical situations such as heart failure and diabetes, improving significantly the rate of adherence to medication with the consequent reduction of events in the follow-up period [43,44]. The role of nurses, pharmacists, and other health agents has been central in these programs aimed at educating and monitoring patients. Its implementation should be cost-effective particularly in low- and middle-income countries. Its limitation lies in the difficulty of performing them on a large scale [43,44].

Another useful intervention is treatment simplification, as it can be assumed that any strategy aimed at simplifying treatment, such as the polypill, will result in improved adherence. Finally, nonadherence is a complex phenomenon with multifactorial origins that requires the combination of several strategies to obtain the best results [45,46]. In addition to the conventional strategies, new approaches have also been adopted to achieve treatment persistence: distribution of informative videos or newsletters by e-mail, multimedia educational programs, medication review with the patient, telemedicine or patient monitoring by video, alarm pill boxes, mobile phone text messages using short message service or multimedia messaging service, and so on [45-47]. A recent meta-analysis showed that mobile phone text messaging approximately doubles the odds of medication adherence. This increase translates into adherence rates improving from 50% (assuming this baseline rate in patients with chronic disease) to 67.8%, or an absolute increase of 17.8%. Though promising, these results should be interpreted with caution given the short duration of trials and reliance on self-reported medication adherence measures [47].

Some studies have shown that complex interventions have provided modest improvements and simple interventions have little or no effect. Most strategies show a loss of efficacy over time, requiring reinforcement strategies [45,46]. It can be assumed that pharmacological adherence will decrease significantly during the first 6 months after prescription, so these months are a critical and decisive period for taking action [48]. A review of publications identified 36 studies with interventions to improve adherence to CV medications in patients with hypertension, dyslipidemia, congestive heart failure, and coronary disease. Of those 36 studies, 17 showed a significant improvement in adherence with the use of behavioral programs, information management, or combined interventions, suggesting that continuous intervention may be necessary for a persistent impact on adherence. Given the diversity of the included studies, the investigators stated that the conclusions should be treated with caution due to the use of indirect comparisons and questions about possible missed studies, the quality of

included data and some review methods (including vote counting) [49,50].

With regard to strategies simplifying treatment, individuals treated with the polypill have higher adherence [51]. Likewise, an opinion survey of CVD patients showed that prescribing a smaller number of tablets, using cards to record blood pressure, self-determination of blood pressure measures, and an explanation of the importance of adherence by the physician are the preferred strategies for improving pharmacological compliance [52].

Recently, the Spanish consensus document on the clinical use of the polypill issued a series of statements related to adherence. Major statements included establishing good doctor-patient communication and relationships, agreeing on the therapeutic plan with the patient to improve their commitment and involvement, simplifying the therapeutic regimen, periodically assessing therapeutic adherence and implementing adherence reinforcement strategies over time. This consensus document also underlines the importance of developing effective and economically affordable drugs and the need for statements for specific populations, such as the elderly, stroke patients, among others [53]. Similarly, the 2016 European guidelines on CV disease prevention [33], the Chilean Society of Cardiology [54], the Argentine Society of Cardiology [55], and the Argentine Federation of Cardiology [56] recommended the use of polypills to increase adherence. Table 4 shows the conclusions and statements developed by the expert panel about adherence in CV medication.

## **POLYPILL: A STRATEGY TO IMPROVE CARDIOVASCULAR DISEASE IN LATIN AMERICA**

### **Polypill: A strategy to optimize adherence and accessibility**

The idea of combining several active compounds in a single drug to reduce CV risk was first proposed more than a decade ago in a document published by WHO [10] and reinforced later by Wald et al. [11]. This concept has not only improved therapeutic convenience and adherence, but it has also optimized health system expenditure.

To date, 4 prospective and randomized clinical trials including 3,835 patients have reported the effects of the polypill on adherence, which was 44% higher in the polypill group than in the control group (74% vs. 53%, 95% confidence interval [CI]: 1.26 to 1.65) [57,58]. These findings are particularly significant because the adherence observed in the comparator groups was significantly higher than expected and generally reported in community observational studies, although this may be due to the Hawthorne (or observer) effect reported in several clinical trials [59]. Thom et al. [60] reported a study in patients with CVD in which adherence with the polypill was better than with the medications administered separately. Adherence among the group of patients who received the polypill was 77% compared with 23% (95% CI: 2.74 to

**TABLE 4.** Statements and conclusions related to adherence to CV medication

No.	Statement/Conclusion	LE/DR	CLA% (n)	DLA % (n)
6.	<p>Treatment nonadherence is a complex, multifactorial phenomenon that includes the following dimensions [13,39,40]:</p> <ul style="list-style-type: none"> <li>• Health system—related: availability, affordability, lack of incentives for health personnel, saturation of the health system.</li> <li>• Disease- or condition-related: chronicity, duration, absence of symptoms, comorbidities.</li> <li>• Treatment-related: polypharmacy, number of tablets, complexity of the treatment, constant changes in regimen, adverse effects.</li> <li>• Patient-related: age, race, marital status, income level, social support, health coverage, educational level, knowledge of the disease, cognitive status, and depression.</li> </ul> <p>In the specific case of CVD, the following barriers are very prevalent:</p> <ul style="list-style-type: none"> <li>• Polypharmacy.</li> <li>• Number of drugs.</li> <li>• Complexity of therapy.</li> <li>• Constant changes in the therapeutic regimen.</li> <li>• Adverse events.</li> <li>• Absence of perception of both treatment benefit and disease severity by the patient.</li> </ul>	2++	100 (9)	100 (27)
7.	<p>Lack of adherence leads to a 35% increase in CV risk events. The increased use of resources derived from these events has a negative impact and raises the cost of treating CVD. Therefore, it is recommended to prioritize the implementation of strategies that increase the adherence rate to essential drugs to reduce CV events and health spending, before implementing new and expensive therapeutic interventions [36].</p>	1+/B	100 (9)	100 (27)
8.	<p>Lack of adherence should be considered as a risk factor for new CV events. Individual factors predisposing to lack of adherence should be systematically investigated in patients who are going to receive chronic CV prevention treatment. (Based on expert opinion.)</p>	4/D	100 (9)	100 (27)

Abbreviations as in Tables 1 and 3.

4.09) in the group receiving the usual treatment [60]. The FOCUS (Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention) study, which included a large number of Latin American patients and who used a polypill composed of ASA, ramipril, and simvastatin, showed a significant increase in adherence in the group that received the polypill regimen compared with those receiving conventional treatment (50.8% vs. 41%, respectively) ( $P = 0.019$ ; intention-to-treat population) [39].

### Polypill and control of risk factors

The polypill containing ASA, ramipril, and a statin has been shown to be equally safe and effective as the same drugs administered separately for the reduction of blood pressure (BP) and total cholesterol, with no significant differences observed at 9 months of follow-up [39]. A significant reduction in systolic BP of 6.3 mm Hg in the polypill group compared with the comparator group (95% CI:  $-9.03$  to  $-3.64$ ) was reported from 13 studies that included 7,638 participants. Eleven studies that included 6,565 participants reported significant reductions in total

cholesterol in the polypill group with levels of 0.61 mmol/l (95% CI:  $-0.88$  to  $-0.35$ ). Moreover, the levels low-density lipoprotein cholesterol (LDL-C) reported from 12 studies and 7,153 participants were lower in the polypill group by 0.70 mmol/l (95% CI:  $-0.98$  to  $-0.41$ ). The authors highlighted that there was a high degree of statistical heterogeneity ( $I^2 \geq 80\%$  for all) that could not be explained, so these results should be considered carefully [57,58]. In the context of primary prevention, a meta-analysis that analyzed 6 trials involving 2,200 patients found that the polypill reduced systolic BP by 9.2 mm Hg (95% CI:  $-13.4$  to  $-5.0$ ), diastolic BP by 5.0 mm Hg (95% CI:  $-7.4$  to  $-2.6$ ) and total cholesterol by 1.22 mmol/l (95% CI:  $-1.60$  to  $-0.84$ ), and LDL-C by 1.02 mmol/l (95% CI:  $-1.37$  to  $-0.67$ ). Although tolerance was lower in those treated with the polypill compared with the placebo group or those receiving a single component, the difference was moderate [61]. In the context of secondary prevention, another meta-analysis analyzing data on 3,140 patients with stable CVD, diabetes, established CVD, or a calculated risk of CVD  $>15\%$  at 5 years, use of the polypill demonstrated better adherence (80% vs. 50%; 95% CI:

1.32 to 1.90) and a significant reduction of systolic BP of  $-2.5$  mm Hg (95% CI:  $-4.5$  to  $-0.4$ ) and LDL-C of  $-0.1$  mmol/l (95% CI:  $-0.2$  to  $0.0$ ) when compared with standard treatment [62].

### Evidence for morbidity and mortality

Five studies that included 5,300 participants reported the effect of the polypill on all-cause mortality and found no significant difference with the control group, although the observed frequency of this event was very low (polypill and control group = 1%; relative risk [RR]: 1.10, 95% CI: 0.64 to 1.89), with a mean follow-up ranging between 9 and 23 months [39,57,60,63-65]. In 6 studies that included 4,517 patients, there were no differences in the rate of fatal and nonfatal atherosclerotic events, and the incidence was also low (4.7% in the intervention group vs. 3.7% in the control group; RR: 1.26; 95% CI: 0.95 to 1.66) [39,57,60,63,64,66,67]. However, none of the clinical trials published to date were designed to evaluate the impact of the polypill on the incidence of serious CV events, such as death, AMI, or stroke.

While waiting for results obtained from studies designed to collect differences in hard events, evidence of the benefit of the polypills comes from meta-analysis and mathematical models. A meta-analysis based on data from 6 primary prevention studies, 21 antihypertensive studies, and 11 studies with statins, applying an additive mathematical model of RR to the Iranian population, concluded that a standard polypill formulation composed of ASA, antihypertensives, and statins could prevent 28,500 AMI deaths and 12,700 stroke deaths [68]. In another study using a mathematical model to calculate the benefit of preventive measures in chronic diseases in England and Wales, the polypill showed a 56% RR reduction for the first AMI or stroke if treatment was started before age 50 [69]. These investigators, using a model where a 4-component polypill had 50% acceptance and 83% adherence, concluded that 990,000 years of life without a first AMI or stroke would be gained each year in the United Kingdom [70].

### Tolerability of polypill

The FOCUS study showed that there were no significant differences in the frequency of adverse events occurring between the group receiving the polypill and the group receiving the 3 drugs separately [39]. A total of 32% of the patients in the control group and 35% in the polypill group had an adverse event. The adverse effect was considered severe in only 6.6% of the control group and 6% of the polypill group, although the study was not designed to show differences in this type of events. Four percent of patients discontinued treatment in both groups. A meta-analysis showed that patients taking the polypill were significantly more likely to discontinue medication (20% vs. 14%; odds ratio: 1.5; 95% CI: 1.2 to 1.9) compared with patients taking placebo or the components alone, although this finding was moderate and there were no

differences among the adverse effects presented (36% vs. 28%; odds ratio: 1.3; 95% CI: 0.7 to 2.5) [61]. In a recently published Cochrane systematic review analyzing 11 studies involving 6,906 patients, no significant differences were found in adverse events reported in the control group and in the group assigned to the polypill (27.1% vs. 31.4%; RR: 1.16; 95% CI: 1.09 to 1.25) [57].

### Polypill and cost-effectiveness

The use of the polypill instead of its separate components over a 10-year period would prevent a total of 46 nonfatal and 11 fatal CV events per 1,000 treated patients. The polypill was also a more effective and cost-effective strategy. The results showed a 90.9% probability that the polypill is a dominant strategy under the hypothesis that the health system was willing to pay €30,000 per quality-adjusted life year (QALY) [71]. The results of a Markov model using data from a clinical trial analyzing the role of the polypill in secondary prevention in the United Kingdom were recently published, and according to the investigators, preventive strategies can result in a gain in lifespan of 2 years [72]. In 6 developing regions (as defined by the World Bank) primary prevention produced an incremental cost-effectiveness ratio of US\$746 to US\$890/QALY gained for patients with an absolute CV risk >25% at 10 years, and US\$1,039 to US\$1,221/QALY gained for those with an absolute CV risk >5%. The incremental cost-effectiveness ratio for secondary prevention ranged from US\$306 to US\$388/QALY gained [73]. Another study evaluated the cost-effectiveness of a polypill composed of 3 antihypertensive drugs, a statin, and ASA for the prevention of CVD in high-risk patients in Latin America. The lifetime risk of CV disease could be reduced by 15% in women and 21% in men if the polypill was used by individuals with a 10-year risk of CV disease  $\geq 15\%$ . Achieving this goal would require treating 26% of the population at a cost of US\$34 to US\$36 per QALY. Offering the polypill to women with high CV risk and men 55 years of age or older would be the best approach and would yield an acceptable incremental cost-effectiveness ratio. The polypill would be very cost-effective even in the country with the lowest GDP of this study. However, health policy makers need to balance the value of the polypill intervention with other interventions, as well as their country's willingness and ability to pay for such interventions [74].

### Strategies to implement the polypill

In the opinion of experts, strategies that can foster the use of the polypill can be divided into several levels. First is the health system level, implemented by improving the accessibility and affordability of the polypill in all levels of medical care. Second is the physician level, implemented by recognizing the consequences of lack of adherence in CV prevention and achieving the involvement of the doctor on the problem of nonadherence, systematically



investigating it in each consultation identifying it and decreasing it with therapeutic and educational strategies such as the use of the polypill, continuing medical education, motivating prescribers to achieve adherence objectives (including remuneration for achieving objectives), promoting this strategy among opinion leaders and scientific societies, and including evidence-based statements for the use of the polypill in clinical practice guidelines. Third is the patient level, implemented by educating the patient on the benefits of using the polypill and involving patient associations in the implementation of the polypill (level of evidence: 4 according to SIGN [14]; level of agreement in the total votes in the consensus meeting: 100%; level of agreement in the total votes in the Delphi-like questionnaire: 100%). Other statements and conclusions related to the polypill as a strategy to improve CV disease in Latin America can be found in Table 5 [75].

## POLYPILL: INDICATIONS FOR USE

### Clinical scenarios in cardiovascular prevention

The conceptual framework for the development of the polypill was clear: to promote greater adherence, accessibility, and efficiency of pharmacological treatment in the largest number of patients worldwide. The recent analysis of the SPACE (Single Pill to Avert Cardiovascular Events) studies shows that patients who benefit most from the

polypill intervention, with systolic BP and LDL-C reductions, are those who were not correctly treated at the beginning of the study [62].

The polypill not only improves patient convenience and adherence, but it also generates health system savings. Although no studies have addressed the optimal moment for starting polypill treatment, experts agree that this therapy should be evaluated if there are foreseen difficulties in patient adherence, accessibility to treatment, or monitoring. A good time to start may also be after an AMI, during the hospitalization (if the patient is in a stable clinical condition), or at discharge, or if a patient has problems with the therapeutic regimen due to complexity or number of tablets [53]. Table 6 shows indications for use of the polypill in primary and secondary prevention.

In addition, treatment with the polypill containing ASA, ACE inhibitors, and statins could be indicated in primary prevention patients with a high or very high CV risk determined by risk charts. Different risk scores have been proposed and developed in several regions with different populations around the world. Although none of them has been calibrated specifically for the population of Latin America, possibly the one that best suits this region is the one proposed by WHO because it takes into account demographic data extracted from American countries. WHO/International Society of Hypertension risk

**TABLE 5.** Statements and conclusions related to the polypill as strategy to improve CVD in Latin America

No.	Statements/Conclusion	LE/DR	CLA% (n)	DLA % (n)
9.	To optimize therapeutic adherence in the prevention of CVD, the following actions are recommended [33,45,46,53]: <ul style="list-style-type: none"> <li>• Simplify the therapeutic regimen by reducing the number of daily doses using the polypill as a public health strategy.</li> <li>• Incorporate educational initiatives.</li> <li>• Ensure drug accessibility and affordability.</li> <li>• Incorporate the use of new technologies such as telemonitoring, electronic devices for patients, text messaging, apps, etc.</li> </ul>	1+/A	100 (9)	100 (27)
10.	Several randomized clinical trials have consistently demonstrated that polypill use significantly improves adherence compared with standard treatment with the same drugs in primary and secondary prevention in different geographic regions, including Latin America [39,60,75].	1+	100 (9)	100 (27)
11.	The polypill reduced blood pressure, total cholesterol, and LDL-C versus placebo in the context of primary prevention [61].	1++	100 (9)	96 (27)
12.	The polypill demonstrated a significant reduction in systolic blood pressure, total cholesterol, and LDL-C, and was as effective as the same drugs administered separately in the context of secondary prevention (patients with stable CVD, diabetes, established CVD, or a calculated 5-yr CVD risk >15%) [62].	1++	100 (9)	96 (27)
13.	Therapeutic inertia is an important barrier in the effective treatment of patients with CVD. The use of fixed-dose drug combinations and/or the polypill, instead of separate titration of each of the essential drugs, is simple and useful tool for overcoming this problem. (Based on expert opinion.)	4/D	100 (9)	100 (27)

LDL-C, low-density lipoprotein cholesterol; other abbreviations as in Table 3.

**TABLE 6.** Indications for use of the Polypill in primary and secondary prevention

<p><b>Primary prevention</b></p> <ul style="list-style-type: none"> <li>- Patients with a high or very high CV risk determined by risk charts.</li> <li>- Diabetic patients older than 50 yrs and at least 1 associated risk factor: smoking, hypertension, dyslipidemia, high LDL-C, or microalbuminuria.</li> <li>- Diabetic patients older than 50 yrs with chronic renal disease and macroalbuminuria or microalbuminuria.</li> </ul>
<p><b>Secondary prevention</b></p> <ul style="list-style-type: none"> <li>- Acute myocardial infarction</li> <li>- Acute coronary syndromes</li> <li>- Stable coronary artery disease</li> <li>- Peripheral artery disease</li> <li>- Stroke</li> <li>- Symptomatic and asymptomatic LVD and high CV risk</li> </ul>

LVD, left ventricular dysfunction; other abbreviations as in [Tables 1 and 5](#).

prediction charts for the Americas (AMR A, B, and D) predict 10-year risk of a fatal or nonfatal major CV event (MI or stroke), according to age, sex, BP, smoking status, total blood cholesterol, and presence or absence of diabetes mellitus. The polypill could be prescribed in patients with 10-year risk of a fatal or nonfatal CV event  $\geq 20\%$  [76]. Also, it could be considered in diabetic patients older than 50 years with low risk of bleeding with ASA and at least 1 associated risk factor, including smoking, hypertension, dyslipidemia, high LDL-C, or microalbuminuria. The data are based on the HOPE (Heart Outcomes Prevention Evaluation) study [77], which showed a benefit in the primary prevention of diabetic patients treated with ramipril, combined with statements from clinical guidelines on the management of diabetic patients [78], and in diabetic patients older than 50 years with chronic renal disease and macroalbuminuria or microalbuminuria [73,74,76]. Finally, the polypill may be of use in patients with high CV risk and clinical or subclinical ventricular dysfunction, in whom ramipril would be prescribed for the cardiac pathology [79] and statin and ASA for the high CV risk.

### Polypill: Limitations and contraindications

Two clinical scenarios could be considered. The first is when therapeutic objectives are not met, and the second is when adverse effects and/or allergies develop. When the therapeutic objectives are not achieved, treatment should be switched to the separate components after ruling out nonadherence. Also, it may be possible to add extra doses of other drugs to achieve the objectives in combination with the polypill. The same strategy could be considered if intolerance develops to 1 of the components of the polypill or if a contraindication emerges to any of the components [53]. Other limitations are related to the possibility of deteriorating lifestyle habits, if the polypill is perceived by

the patient as a panacea. In this regard, 3 studies (UMPIRE [Use of a Multidrug Pill in Reducing Cardiovascular Events], IMPACT (IMProving Adherence using Combination Therapy), and Kanyini-GAP [Kanyini Guidelines Adherence With the Polypill] [60,63,64]) collected lifestyle behavioral data (specifically weight, abdominal circumference, body mass index, and duration of physical activity) and did not find significant differences between patients treated with the polypill compared with those in the control group. Statements and conclusions related to the indication for use of the polypill are depicted in [Table 7](#) [80,81].

### Discussion

Although the concept of the therapeutic polypill has been around for a while, its implementation in CVD has been slow compared with in other diseases for several reasons, including the resistance of the health systems and physicians to adopt its use. The use of fixed doses with the consequent impossibility of titration is possibly among the main barriers in the implementation of the polypill by physicians. Although in hypertensive patients, the polypill available in Latin America is available in 2 different doses, failure to reach the expected goals may be a limitation for its indication. However, the rate of use of essential drugs in secondary prevention, especially in low- and middle-income countries, is so low in our region that even in suboptimal doses, its use on a large scale would have an enormous impact in terms of benefit.

The aim of this document was to gather and present the evidence related to nonadherence as a public health problem in our countries and specifically to address how polypill as intervention can help in Latin America to improve CV care at individual and population levels, reducing the lack of adherence. This is the main aspect in which it differs from the other recently published polypill consensus statements [53].

The clinical questions that served as the basis for this document were answered with a series of relevant publications selected by the expert panel and completed with a nonexhaustive systematic search whenever the recovered evidence was incomplete. Although this consensus was not reached exclusively with a systematic review of the publications, opening up the possibility of selection bias, the quality of the selected publications ensures a strong framework, and the subsequent systematic procedure ensures that the most important evidence published in the field is reflected in the document. One issue that emerged during the preparation of the document is the partial lack of epidemiological studies focusing on CVDs in Latin America, so we were forced to use data generated in other world regions. This type of study must be conducted in the Latin American setting to allow the medical community and governments to take informed actions to control the CVD epidemic in the region. Only then will the implicated players be able to offer their communities the best options

**TABLE 7.** Statements and conclusions related to the indication for use of the polypill

No.	Statements/Conclusion	LE/DR	CLA% (n)	DLA % (n)
14.	Based on study results measuring the impact of increased adherence using mathematical models, a significant reduction in the number of major CV events and CV mortality is expected with the use of the polypill. Studies should be designed and conducted in Latin America to analyze the impact of increased adherence with the polypill and the corresponding benefits. (Based on expert opinion.)	4	100 (9)	100 (27)
15.	In studies conducted with the polypill, no significant increase is observed in serious adverse events compared with the drugs administered separately [39].	1+	100 (9)	100 (27)
16.	In case of an adverse event potentially due to 1 of the components of polypill, discontinuation of the polypill and identification of the component that generated the adverse event is recommended. Subsequently, the other components may be reintroduced and the causative component may be replaced. (Based on expert opinion.)	4/D	100 (9)	100 (27)
17.	According to cost-effectiveness models, the polypill is cost-effective compared with standard treatment in different settings and would therefore provide significant savings to health systems in CVD prevention [71,72,74].	4	100 (9)	100 (27)
18.	The implementation of a strategy based on the use of the polypill, which incorporates in single daily dose some of the drugs that have demonstrated efficacy in CV risk reduction, is recommended for secondary CV prevention (patients who have presented acute or chronic ischemic heart disease, revascularized or not, with cerebral or peripheral atherothrombotic disease), unless any of the components is contraindicated [80,81].	1+/A	100 (9)	100 (27)
19.	Until results are available from larger studies that demonstrate strong scientific evidence, the systematic use of the polypill for all patients in primary prevention is not recommended. However, it may be considered in high-risk patients with an indication for all the drugs included in the polypill available in the region. (Based on expert opinion.)	4/D	100 (9)	100 (27)

Abbreviations as in Tables 1 and 3.

and interventions, tailored to their necessities and expectations, thus fulfilling the main requirements for a successful outcome.

The polypill represents a unique opportunity to implement a public health program based on improving adherence to existing medicines with proven efficacy and also to improve accessibility and affordability of these medicines in Latin America. This intervention could help relieve the individual and social burden of CVD. The Latin American countries cannot rely on reductionist solutions to halt the increase of CVD in the region; instead they must implement a holistic program that involves several players, ranging from physicians to governments, who need to orchestrate the most appropriate response to this challenge.

## Conclusions

The expert committee recognizes that nonadherence to medical therapy is a big problem and recommends the incorporation of the polypill in public health programs for CV prevention. Based on the knowledge of the expert

panel, and at the time of writing, the only polypill approved and available in some Latin American countries (Argentina, Chile, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, and Paraguay as shown in Table 1) consists of ASA, simvastatin/atorvastatin, and ramipril (level of evidence: 4; level of agreement in the total votes in the consensus meeting: 100%; level of agreement in the total votes in the Delphi-like questionnaire: 100%).

Improving adherence to treatment should be a primary objective in the attempt to reduce premature CV mortality. The generation of continuous medical education programs, the production and dissemination of simple, friendly, and reliable information for patients and their families and the simplification of treatments through the polypill, emerge as powerful strategies in the region. The Inter American Society of Cardiology is firmly committed to these actions. Interaction with other organizations in the region such as the Pan American Health Organization, World Heart Federation, and Inter American Heart Foundation is essential in the control of risk factors and the promotion of CV health. Finally, alliances between scientific societies,

patient associations, and government are essential to achieving the 25 × 25 goal.

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### REFERENCES

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1459–544.
2. Lanas F, Avezum A, Bautista LE, et al. Risk factors for acute myocardial infarction in Latin America: the INTERHEART Latin American study. *Circulation* 2007;115:1067–74.
3. Tunstall-Pedoe H, editor. Preventing Chronic Diseases: A Vital Investment: WHO Global Report. Geneva, Switzerland: World Health Organization; 2005.
4. Rodríguez T, Malvezzi M, Chatenoud L, et al. Trends in mortality from coronary heart and cerebrovascular diseases in the Americas: 1970–2000. *Heart* 2006;92:453–60.
5. Ezzati M, Obermeyer Z, Tzoulaki I, Mayosi BM, Elliott P, Leon DA. Contributions of risk factors and medical care to cardiovascular mortality trends. *Nat Rev Cardiol* 2015;12:508–30.
6. Fleischer NL, Diez Roux AV. [Inequities in cardiovascular diseases in Latin America]. *Rev Peru Med Exp Salud Publica* 2013;30:641–8.
7. Pan American Health Organization (PAHO). Hoja informativa: Enfermedades crónicas en las Américas. (30 de noviembre de 2009). Available at: [http://www1.paho.org/hq/dmdocuments/2009/hoja\\_info\\_julio\\_09\\_ECNT\\_Capitol\\_Hill.pdf](http://www1.paho.org/hq/dmdocuments/2009/hoja_info_julio_09_ECNT_Capitol_Hill.pdf). Accessed April 1, 2016.
8. Organización Mundial de la Salud (OMS), Organización Panamericana de la Salud (OPS). Prevención de las enfermedades cardiovasculares: directrices para la evaluación y el manejo del riesgo cardiovascular. Available at: [http://www.paho.org/hq/index.php?option=com\\_docman&task=doc\\_view&gid=13815&Itemid=270](http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=13815&Itemid=270); 2007. Accessed April 1, 2018.
9. Kronish IM, Ye S. Adherence to cardiovascular medications: lessons learned and future directions. *Prog Cardiovasc Dis* 2013;55:590–600.
10. WHO. Secondary prevention of noncommunicable diseases in low- and middle-income countries through community-based and health service interventions: World Health Organization-Wellcome Trust meeting report, 1–3 August 2001. Geneva, Switzerland: World Health Organization; 2002.
11. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419.
12. Webster R, Castellano JM, Onuma OK. Putting polypills into practice: challenges and lessons learned. *Lancet* 2017;389:1066–74.
13. Castellano JM, Sanz G, Fernandez Ortiz A, Garrido E, Bansilal S, Fuster V. A polypill strategy to improve global secondary cardiovascular prevention: from concept to reality. *J Am Coll Cardiol* 2014;64:613–21.
14. Scottish Intercollegiate Guidelines Network. SIGN 50: A Guideline Developers' Handbook. Edinburgh, UK: SIGN, 2004. Available at: [https://www.sign.ac.uk/assets/sign\\_grading\\_system\\_1999\\_2012.pdf](https://www.sign.ac.uk/assets/sign_grading_system_1999_2012.pdf). Accessed September 1, 2016.
15. Yusuf S, Hawken S, Ounpuu S, et al., for the INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937–52.
16. O'Donnell MJ, Xavier D, Liu L, et al., for the INTERSTROKE Investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010;376:112–23.
17. O'Donnell MJ, Chin SL, Rangarajan S, et al., for the INTERSTROKE Investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* 2016;388:761–75.
18. Schargrofsky H, Hernandez-Hernandez R, Champagne BM, et al., for the CARMELA Study Investigators. CARMELA: assessment of cardiovascular risk in seven Latin American cities. *Am J Med* 2008;121:58–65.
19. Palmira Pramparo CB, Schargrofsky H, for the CARMELA Study Investigators. Evaluación del riesgo cardiovascular en siete ciudades de Latinoamérica: las principales conclusiones del estudio CARMELA y de los subestudios. *Rev Argent Cardiol* 2011;79:377–82.
20. Yusuf S, Rangarajan S, Teo K, et al., for the PURE Investigators. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med* 2014;371:818–27.
21. WHO Guidelines Approved by the Guidelines Review Committee. WHO Guideline on Country Pharmaceutical Pricing Policies. WHO Guidelines Approved by the Guidelines Review Committee. Geneva, Switzerland: World Health Organization; 2013.
22. Avezum A, Oliveira GBF, Lanas F, et al. Secondary CV prevention in South America in a community setting: the PURE study. *Glob Heart* 2017;12:305–13.
23. Yusuf S, Islam S, Chow CK, et al., for the PURE Study Investigators. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE study): a prospective epidemiological survey. *Lancet* 2011;378:1231–43.
24. PAHO. Health in the Americas: Health Systems and Social Protection in Health. Washington, DC: Pan American Health Organization; 2012.
25. Bocchi EA, Arias A, Verdejo H, et al. for the Interamerican Society of Cardiology. The reality of heart failure in Latin America. *J Am Coll Cardiol* 2013;62:949–58.
26. Glassman A, Gaziano TA, Bouillon Buendia CP, Guanais de Aguiar FC. Confronting the chronic disease burden in Latin America and the Caribbean. *Health Aff (Millwood)* 2010;29:2142–8.
27. Pachman ML, Pugb JA, Romero RL, Bowers KW. Competing demands or clinical inertia: The case of elevated glycosylated haemoglobin. *Ann Intern Med* 2007;5:196–201.

28. Whitford DL, Al-Anjawi HA, Al-Baharna MM. Impact of clinical inertia on cardiovascular risk factors in patients with diabetes. *Primary Care Diabetes* 2014;8:133–8.
29. Morales C, Mauri M, Vila L. Vencer la inercia terapéutica en el manejo del paciente dislipidémico: Un reto en la práctica clínica diaria. *Clin Invest Arterioscl* 2014;26:193–9.
30. Phillips LS, Branch WT, Cook CB, et al. Clinical inertia. *Ann Intern Med* 2001;135:825–34.
31. López-Simarro F. Inercia terapéutica. Causas y soluciones. *Hipertension y Riesgo Vascular* 2012;29:28–33.
32. Khatib R, McKee M, Shannon H, et al., for the PURE Study Investigators. Availability and affordability of cardiovascular disease medicines and their effect on use in high-income, middle-income, and low-income countries: an analysis of the PURE study data. *Lancet* 2016;387:61–9.
33. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; 37:2315–81.
34. WHO. Adherence to long-term therapies: evidence for action. Geneva, Switzerland: World Health Organization; 2003.
35. Rodriguez F, Cannon CP, Steg PG, et al., for the REACH Registry Investigators. Predictors of long-term adherence to evidence-based cardiovascular disease medications in outpatients with stable atherosclerotic disease: findings from the REACH Registry. *Clin Cardiol* 2013;36:721–7.
36. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013;34:2940–8.
37. Choudhry NK, Glynn RJ, Avorn J, et al. Untangling the relationship between medication adherence and post-myocardial infarction outcomes: medication adherence and clinical outcomes. *Am Heart J* 2014;167:51–58.e5.
38. Bansilal S, Castellano JM, Garrido E, et al. Assessing the impact of medication adherence on long-term cardiovascular outcomes. *J Am Coll Cardiol* 2016;68:789–801.
39. Castellano JM, Sanz G, Penalvo JL, et al. A polypill strategy to improve adherence: results from the FOCUS project. *J Am Coll Cardiol* 2014; 64:2071–82.
40. Choudhry NK, Fischer MA, Avorn J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. *Arch Intern Med* 2011;171:814–22.
41. Bitton A, Choudhry NK, Matlin OS, Swanton K, Shrank WH. The impact of medication adherence on coronary artery disease costs and outcomes: a systematic review. *Am J Med* 2013;126:357.e7–357.e27.
42. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. *Health Aff (Millwood)* 2011;30:91–9.
43. Sosa Liprandi MI, Sosa Liprandi A. Utilidad de las clínicas de transición en el manejo ambulatorio de la insuficiencia cardíaca. In: Martínez FA, Perna E, Perrone S, editors. *Manejo práctico de la insuficiencia Cardíaca*. Buenos Aires, Argentina: Silver Horse; 2018. p. 19–25.
44. Feltner C, Jones CD, Cene CW, et al. Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis. *Ann Intern Med* 2014;160:774–84.
45. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. *Annu Rev Pharmacol Toxicol* 2012;52:275–301.
46. Murray MD, Young J, Hoke S, et al. Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. *Ann Intern Med* 2007;146:714–25.
47. Adler AJ, Martin N, Mariani J, et al. Mobile phone text messaging to improve medication adherence in secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2017;4:CD011851.
48. Gonzalez-Juanatey JR, Mostaza JM, Lobos JM, Abarca B, Listerri JL. A step ahead in secondary prevention of cardiovascular risk: consensus document on clinical use of the polypill. *Rev Esp Cardiol (Engl Ed)* 2016;69:547–50.
49. van Dalem J, Krass I, Aslani P. Interventions promoting adherence to cardiovascular medicines. *Int J Clin Pharm* 2012;34:295–311.
50. Santo K, Kirkendall S, Laba TL, et al. Interventions to improve medication adherence in coronary disease patients: a systematic review and meta-analysis of randomised controlled trials. *Eur J Prev Cardiol* 2016;23:1065–76.
51. Laufs U, Rettig-Ewen V, Bohm M. Strategies to improve drug adherence. *Eur Heart J* 2011;32:264–8.
52. Márquez Contreras E, Martell Claros N, Gil Guillén V, et al. El uso de fármacos en combinación a dosis fijas en el tratamiento de las enfermedades cardiovasculares. Fármacos en combinación a dosis fijas y cumplimiento en el tratamiento de las enfermedades cardiovasculares: Asociación de la Sociedad Española de Hipertensión y Liga Española para la Lucha contra la HTA y SAHTA y RV. p. 47.
53. González-Juanatey J, Mostaza J, Lobos J, et al. Nuevo enfoque terapéutico para la prevención secundaria del riesgo cardiovascular: Documento de consenso del uso clínico de la Polypill. 2016. Available at: [http://www.revespcardiol.org/contenidos/static/docs/Consenso%20Polypill\\_v4\\_2.pdf](http://www.revespcardiol.org/contenidos/static/docs/Consenso%20Polypill_v4_2.pdf). Accessed October 1, 2016.
54. Vejar M, Abufhele A, Varleta P, et al. Adherencia farmacológica y prevención secundaria cardiovascular: una de las principales barreras en el tratamiento de la enfermedad aterosclerótica. Posición del Departamento de Prevención Cardiovascular de SOCHICAR en el uso de la polipíldora en prevención secundaria. *Rev Chilena Cardiol* 2016;35:270–82.
55. Sosa Liprandi A, Martínez F, Sosa Liprandi M, et al. Rol de la Polipíldora como estrategia de prevención cardiovascular en Argentina. *Rev Argent Cardiol* 2017;85:9.
56. Sosa Liprandi A, Martínez F, Sosa Liprandi M, et al. Rol de la polipíldora como estrategia de prevención cardiovascular en Argentina. Role of the polypill as a cardiovascular prevention strategy in Argentina. *Rev Fed Arg Cardiol* 2017;46:9.
57. Bahiru E, de Cates AN, Farr MR, et al. Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases. *Cochrane Database Syst Rev* 2017;3:CD009868.
58. Huffman MD, Xavier D, Perel P. Uses of polypills for cardiovascular disease and evidence to date. *Lancet* 2017;389:1055–65.
59. Davis SA, Feldman SR. Using Hawthorne effects to improve adherence in clinical practice: lessons from clinical trials. *JAMA Dermatol* 2013;149:490–1.
60. Thom S, Poulter N, Field J, et al., for the UMPIRE Collaborative Group. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. *JAMA* 2013;310:918–29.
61. Elley CR, Gupta AK, Webster R, et al. The efficacy and tolerability of 'polypills': meta-analysis of randomised controlled trials. *PLoS One* 2012;7:e52145.
62. Webster R, Patel A, Selak V, et al., for the SPACE Collaboration. Effectiveness of fixed dose combination medication ('polypills') compared with usual care in patients with cardiovascular disease or at high risk: a prospective, individual patient data meta-analysis of 3140 patients in six countries. *Int J Cardiol* 2016;205:147–56.
63. Selak V, Elley CR, Bullen C, et al. Effect of fixed dose combination treatment on adherence and risk factor control among patients at high risk of cardiovascular disease: randomised controlled trial in primary care. *BMJ* 2014;348:g3318.
64. Patel A, Cass A, Peiris D, et al., for the Kanyini GAP Collaboration. A pragmatic randomized trial of a polypill-based strategy to improve use of indicated preventive treatments in people at high cardiovascular disease risk. *Eur J Prev Cardiol* 2015;22:920–30.
65. Zamorano J, Erdine S, Pavia A, et al., for the CRUCIAL Investigators. Proactive multiple cardiovascular risk factor management compared

- with usual care in patients with hypertension and additional risk factors: the CRUCIAL trial. *Curr Med Res Opin* 2011;27:821–33.
66. Malekzadeh F, Marshall T, Pourshams A, et al. A pilot double-blind randomised placebo-controlled trial of the effects of fixed-dose combination therapy (“polypill”) on cardiovascular risk factors. *Int J Clin Pract* 2010;64:1220–7.
  67. Park JS, Shin JH, Hong TJ, et al. Efficacy and safety of fixed-dose combination therapy with olmesartan medoxomil and rosuvastatin in Korean patients with mild to moderate hypertension and dyslipidemia: an 8-week, multicenter, randomized, double-blind, factorial-design study (OLSTA-D RCT: Olmesartan rosuvaSTatin from Daewoong). *Drug Des Devel Ther* 2016;10:2599–609.
  68. Sepanlou SG, Farzadfar F, Jafari E, Danaei G. Cardiovascular disease prevention using fixed dose pharmacotherapy in Iran: updated meta-analyses and mortality estimation. *Arch Iran Med* 2012;15:531–7.
  69. Wald NJ, Morris JK. Quantifying the health benefits of chronic disease prevention: a fresh approach using cardiovascular disease as an example. *Eur J Epidemiol* 2014;29:605–12.
  70. Wald NJ, Luteijn JM, Morris JK, Taylor D, Oppenheimer P. Cost-benefit analysis of the polypill in the primary prevention of myocardial infarction and stroke. *Eur J Epidemiol* 2016;31:415–26.
  71. Barrios V, Kaskens L, Castellano J, et al. Utilidad de un policomprimido cardiovascular en el tratamiento de pacientes en prevención secundaria en España: un estudio de coste-efectividad. *Revista Española de Cardiología*. 2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/?term=Barrios+V%2C+Kaskens+L%2C+Castellano+J%2C+Cosin-Sales+J%2C+Ruiz+J%2C+Zsolt+I%2C>. Accessed March 1, 2018.
  72. Becerra V, Gracia A, Desai K, et al. Cost-effectiveness and public health benefit of secondary cardiovascular disease prevention from improved adherence using a polypill in the UK. *BMJ Open* 2015;5:e007111.
  73. Gaziano TA, Opie LH, Weinstein MC. Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. *Lancet* 2006;368:679–86.
  74. Bautista LE, Vera-Cala LM, Ferrante D, et al. A “polypill” aimed at preventing cardiovascular disease could prove highly cost-effective for use in Latin America. *Health Aff (Millwood)* 2013;32:155–64.
  75. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med* 2007;120:713–9.
  76. WHO. Prevention of Cardiovascular Disease: Pocket Guidelines for Assessment and Management of Cardiovascular Risk. 2007. Available at: [http://www.who.int/cardiovascular\\_diseases/guidelines/PocketGL-ENGLISH.AFR-D-E.rev1.pdf](http://www.who.int/cardiovascular_diseases/guidelines/PocketGL-ENGLISH.AFR-D-E.rev1.pdf). Accessed November 1, 2016.
  77. Yusuf S, Sleight P, Pogue J, et al., for the Heart Outcomes Preventions Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145–53.
  78. Standards of medical care in diabetes—2017: summary of revisions. *Diabetes Care* 2017;40 Suppl 1:S4–5.
  79. Volpe M. Should all patients at high cardiovascular risk receive renin-angiotensin system blockers? *QJM* 2012;105:11–27.
  80. Castellano JM, Copeland-Halperin R, Fuster V. Aiming at strategies for a complex problem of medical nonadherence. *Glob Heart* 2013;8:263–71.
  81. Fuster V, Martínez F. Las intervenciones terapéuticas que generan más expectativas para la próxima década. *Rev Fed Arg Cardiol* 2015;44:67–76.

**ONLINE APPENDIX 1****Relevant clinical questions developed by the experts in the kickoff meeting**

Q1: What risk factors are associated with cardiovascular disease and its comorbidities? What is its prevalence in Latin America?

Q2: What is the clinical impact of the different risk factors on cardiovascular disease in Latin America?

Q3: Does the GDP of Latin American countries affect the rate of use of essential drugs for the secondary prevention of cardiovascular disease?

Q4: What is the rate of use of essential drugs for the secondary prevention of cardiovascular disease in Latin America?

Q5: In terms of availability, accessibility, and affordability, what barriers exist to access essential drugs for the secondary prevention of cardiovascular disease in Latin America?

Q6: What factors determine the lack of therapeutic adherence in primary and secondary prevention of cardiovascular disease?

Q7: What consequences have for patients, health care professionals and the health system the lack of therapeutic adherence in primary and secondary prevention of cardiovascular disease?

Q8: What actions can be taken to optimize therapeutic adherence in prevention of cardiovascular disease?

Q9: How does the therapeutic inertia affect the prevention of cardiovascular disease?

Q10: What benefits are expected from the Polypill in terms of increasing the therapeutic adherence of patients subject to primary or secondary cardiovascular prevention?

Q11: What data exist regarding the availability, accessibility, and affordability of the Polypill?

Q12: From the point of view of the doctor and the patient what factors can enhance the use of the Polypill?

Q13: What benefits are expected from the Polypill in terms of controlling the clinical and biochemical parameters of patients subject to cardiovascular prevention?

Q14: What benefits are expected from the Polypill in terms of morbidity and mortality of patients subject to cardiovascular prevention?

Q15: What benefits are expected from the Polypill in terms of the rate of adverse effects in patients subject to cardiovascular prevention?

Q16: What benefits are expected from the Polypill in terms of the treating cost of patients on cardiovascular prevention?

Q17: What type of patients could benefit from the Polypill in secondary prevention?

Q18: What parameters and values define the patient with high and very high cardiovascular risk?

Q19: What type of patients with high cardiovascular risk could benefit from the Polypill in primary prevention?

Q20: What type of patients with high cardiovascular risk could benefit from the three components of the Polypill in primary prevention?

Q21: How should one act in front of a patient showing adverse effects to any of the components of the Polypill?

Q22: What are the drawbacks and risks derived from administering fixed doses through the Polypill?

Q23: In which patient profiles would not be indicated the use of the Polypill?

Q24: In which moment should the Polypill be prescribed?

**ONLINE APPENDIX 2****Search sequence used in PubMed used to gather information related to question 9**

Cardiovascular Diseases[Mesh] AND ("prevention and control" [Subheading] OR "Secondary Prevention"[Mesh] OR "Primary Prevention"[Mesh]) AND (("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND inertia[Title]) AND "last 5 years"[PDat] AND (English[lang] OR Spanish[lang])