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Embracing the polypill as a cardiovascular therapeutic: is this the best strategy?

EMBRACING THE POLYPILL AS A CARDIOVASCULAR THERAPEUTIC: IS THIS THE BEST STRATEGY?

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ABSTRACT:

Introduction: Cardiovascular disease (CVD) is an important cause of mortality and morbidity worldwide. CVD morbidity and mortality are associated with significant financial costs related to hospitalization, medication, and lost productivity. The concept of the 'polypill' for the reduction of cardiovascular risk was proposed in 2000. A polypill is a fixed combination of drugs in a single tablet or capsule. The initial polypill consisted of three different classes of antihypertensive drugs (each at half dose), in addition to aspirin, a statin, and folic acid. The challenge today is to produce polypills containing drugs with established efficacy and complementary actions.

Areas covered: The authors provide their expert perspectives on the polypill and consider the randomized clinical trials that have evaluated the safety, efficacy, adherence and cost-effectiveness of polypills.

Expert opinion: The polypill makes prescribing easier by reducing the need for complex treatment algorithms and dose titration. It also appears to be cost-effective. However, there are several issues that need to be addressed before the polypill can be used routinely. A single polypill formulation may not be suitable for all patients. It may be necessary to develop several types of polypill to meet the needs of different patient groups.

Keywords: polypill, cardiovascular disease, primary and secondary prevention

1. 1. Introduction

Cardiovascular disease (CVD) is an important cause of mortality and morbidity worldwide. According to estimates, 25 million people in total will die of CVD by 2030 [1]. Although CVD mortality rate has declined in high-income countries, it has continued to rise in low- and middle-income countries. The rate of premature deaths from CVD ranges from 4% in high-income countries to 42% in low-income countries [2,3]. CVD morbidity and mortality are associated with significant financial costs related to hospitalization, medication, and lost productivity. This CVD epidemic is linked to increased prevalence of well-established, modifiable risk factors such as hypertension, diabetes, obesity, dyslipidemia, physical inactivity, poor diet, and tobacco use [3]. Large epidemiological studies have demonstrated that the aforementioned risk factors account for as much as 90% of CVD events [4].

1. 2. Areas covered

1. 2.1. The concept of the polypill

The concept of the ‘polypill’ for the reduction of cardiovascular risk was proposed by Wald and Law [5] in 2000. A polypill is a fixed combination of drugs in a single tablet or capsule. The initial polypill consisted of three different classes of antihypertensive drugs (each at half dose), in addition to aspirin, a statin, and folic acid. The challenge today is to produce polypills containing drugs with complementary actions and established efficacy in the reduction of modifiable risk factors for CVD [3].

According to estimates made by Wald and Law, the polypill reduces ischemic heart

disease (IHD) events by 88% and strokes by 80% compared with placebo. Moreover, they suggested that it could be used without needing to consider concomitant risk factors. The polypill was developed in order to enhance accessibility, effectiveness of medicines and to improve patient adherence. This would be expected to improve cost-effectiveness [6]. Numerous randomized controlled trials (RCTs) have evaluated the safety, efficacy, adherence and cost-effectiveness of polypills.

The selection of the constituent drugs to be included in a polypill is a complicated matter. Clinical evidence relating to the efficacy of the treatments for known modifiable CVD risk factors and the prevalence of adverse events should be considered [3]. The doses of drugs in polypills are selected in order to achieve the optimal balance between efficacy and safety [6]. Wald and Law performed a meta-analysis to calculate the relative risk reduction associated with each individual component of the polypill [7]. Their formulation contained off-patent medicines in order to reduce cost. These drugs were used at modest doses to reduce the prevalence of adverse effects (AEs). The polypill proposed by Wald and Law can be used in both primary and secondary prevention of CVD and contains low-dose aspirin (50 to 125 mg/d), folic acid 0.8 mg/d, a potent statin (e.g., atorvastatin 10 mg or simvastatin 40 to 80 mg), and three blood pressure (BP)-lowering drugs at half the standard dose (chosen from thiazide diuretics, beta-blockers, angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and calcium channel blockers) [7]. However, the results of clinical studies have changed attitudes towards some of the drugs initially suggested for inclusion in polypills. For example, large randomized controlled trials have shown no benefit of folic acid in preventing CVD [8]. Low-dose aspirin has been shown to be beneficial only in secondary prevention [9]. In the ASPREE trial in the healthy elderly, primary prevention with aspirin (100mg daily) led to a significantly increased risk of bleeding, without reduced risk of CVD [10]. The ARRIVE RCT showed no benefit of aspirin (100mg daily) in the primary prevention CVD in 12,000 non-diabetic adults with multiple risk factors for CVD [11]. In the ASCEND trial of aspirin (100mg daily) for the primary prevention of CVD in participants with diabetes, aspirin reduced the risk of vascular events, but this benefit was negated by the increased bleeding hazard [12]. Interestingly, it has recently been demonstrated that low dose aspirin (<100mg/day) may only be effective in the primary prevention of aspirin in patients weighing <70mg, and that tailoring aspirin dose by body weight may be necessary [13]. Whilst this approach has the potential to

improve the efficacy of aspirin in primary prevention, tailored dosing would be hard to a achieve in a polypill. The evidence supporting other polypill components has increased. Recent studies have confirmed the importance of statins, demonstrating that each 1-mmol/L reduction in LDL-cholesterol over 5 years is associated with a 11% relative risk reduction in total mortality, 26% in major ischemic heart disease (IHD) events and 16% in strokes [14]. Statin treatment may occasionally result in myopathy, rhabdomyolysis and persistent elevation in transaminases [15]. It is also associated with a slightly elevated risk of developing diabetes mellitus [16]. In a meta-analysis conducted by Wald and Law, the use of lovastatin (40 mg), simvastatin (40 mg), or atorvastatin 10 mg was associated with absolute reduction in low-density lipoprotein (LDL) cholesterol by 37%. From this, the authors predicted a 52% relative risk reduction in ischemic heart disease and a 17% relative risk reduction in stroke [3,17]. Wald and Law assumed that the combination of three different antihypertensive agents used at half of the standard doses would safely reduce BP, resulting in a reduction in the prevalence of strokes by 63% and IHD by 46% [18]. The goal of combining several drugs at low doses was to minimize the side effects observed at high doses, whilst maintaining efficacy. Moreover, the combination of drugs could help counterbalance their side effects, e.g. the inclusion of renin-angiotensin system blockers in the polypill could help to avoid the hypokalemia and hyperglycemia which might be expected from the concurrent administration of diuretics [7]. On the basis of the analysis of RCTs Wald and Law suggested that using three antihypertensive drugs in combination and at low doses would reduce diastolic blood pressure (DBP) by 11 mmHg and reduce the risk for ischemic heart disease by 46% and stroke by 63%. Wald and Law suggested that the formulation should contain 6 different compounds in order to maximize potential benefits.

The formulation and manufacturing of a tablet or capsule containing so many active compounds presents several challenges. Problems accumulate as the number of active ingredients increases. Each additional drug increases the possibility for more AEs. Therefore, using too many components could limit the potential patient population [3]. Wald and Law estimated that the rate of adverse effects of the polypill would range between 8% and 15% [5]. However, the actual rates of adverse effects of long-term treatment with a polypill are not known. Formulation of polypills is made more challenging by the range of different chemical and physical characteristics of the components. For example, it can be difficult to combine compounds with differing solubility and sensitivity to heat and moisture. The range of doses (e.g.

ramipril at 2.5 mg and atenolol at 100 mg) can also prove challenging. The potential for drug-drug interactions and the bioavailability of components should also be considered in the preparation of a polypill. Bioavailability, and the achievement of appropriate plasma drug concentrations can pose a real difficulty. Patel *et al.* [19] demonstrated that simvastatin efficacy was significantly lower when simvastatin was taken as a part of the Polycap pill (simvastatin 20 mg, aspirin 100 mg, hydrochlorothiazide [HCTZ] 12.5 mg, atenolol 50 mg, ramipril 5 mg) than when it was taken alone. However, surprisingly, the bioavailability of the active metabolite of simvastatin was demonstrated to be higher when taken in the combination formulation. **Table 1** summarizes currently available polypills.

Table 1. The summary of currently available polypills working on several risk factors/conditions both for primary and secondary preventions.

Product	**Company**	**Composition**	**Indication**	**Country**
Polycap	Cadila Pharma	Aspirin (100 mg), atenolol (50 mg), thiazide (12.5 mg), ramipril (5 mg) and simvastatin (20 mg)	Primary prevention	India, Zambia
Trinomia/Sincronium/ Iltria	Ferrer	Aspirin (100 mg), ramipril (2.5 mg; 5 mg; 10 mg) and either simvastatin (40 mg) or atorvastatin (20 mg)	Secondary prevention	Austria, Belgium, Bulgaria, Czech rep. Germany, Finland, France, Greece, Ireland, Italy, Poland, Portugal, Romania, Spain, Sweden Guatemala, Honduras, Dominican Republic, El Salvador, Nicaragua, Argentina, Chile, Paraguay, Ecuador, Mexico
Zycad-4	ZydusCardiva	Aspirin (75 mg), atorvastatin (10 mg), ramipril (5 mg) and metoprolol (50 mg) which is supplied as separate pill	Secondary prevention	India
Polytorva	USV	Aspirin (75 mg), atovastatin (5 mg) and ramipril (10 mg)	Secondary prevention	India
Ramitorva	ZydusCardiva	Aspirin (75 mg), atovastatin (10 mg) and ramipril (5 mg)	Secondary prevention	India
Polypill	Cipla, India	Amlodipine (2.5 mg), losartan (25 mg), hydrochlorothiazide	Primary prevention	No market approval

		(12.5 mg) and simvastatin (40 mg)		
Red Heart Pill 1™	Dr Reddy's Laboratories	Aspirin (75 mg), lisinopril (10 mg), simvastatin (20 mg) and atenolol (50 mg)	Secondary prevention	No market approval
Red Heart Pill 2™	Dr Reddy's Laboratories	Aspirin (75 mg), lisinopril (10 mg), simvastatin (20, 40 mg) and hydrochlorothiazide (12.5 mg)	Secondary prevention	No market approval
PolyIran	Alborz Darou (Iran)	Aspirin (81 mg), atorvastatin (20 mg), enalapril (5 mg) or valsartan (40 mg) and hydrochlorothiazide (12.5 mg)	Primary/ secondary prevention	No market approval

1. 2.2. Use of the Polypill in primary prevention

Primary prevention should encompass multiple strategies, including: health policy and environmental changes, individual behavioral changes, and the use of drugs with proven efficacy and safety [7]. Behavioral interventions aiming at the alteration of individual lifestyles are costly, exert only modest and unsustainable impact, and have failed to reduce the occurrence of CVD events in large trials [7,20]. Changes in health policy, the environment, and cultural attitudes exert a greater impact. However, such interventions are not implemented in most developed and developing countries. Primary prevention can be approached at both individual and population levels [7]. In the individual approach, screening is used to identify high-risk individuals to enable effective risk-management. Such "tailoring" of an intervention to each individual is expected to optimize benefits and risks. However, it is also associated with high screening costs and imprecise risk prediction in primary prevention, especially when calculating long-term risk. Primary prevention should also consider the recognized relationship between modifiable risk factors (BP, LDL, cholesterol, smoking) and CVD [21-23]. The use of drugs to reduce the severity of these risk factors is a complementary approach. Long-term administration of multiple drugs to "healthy" asymptomatic individuals in order to lower multiple risk factor levels is impractical and it can succeed only when individuals are exceptionally motivated. However, a fixed-dose combination drug, administered once daily (i.e., a polypill), which simultaneously modifies several risk factors and probably reduces CVD may enjoy an enthusiastic uptake. In

people without CVD, age is the most discriminatory screening factor. Therefore, the use of a polypill in people aged >55 years, (particularly in those with at least one additional risk factor) could prevent the majority of CVD events in both high- and low-income countries [7].

Several clinical trials have assessed the utility of the polypill in primary prevention. A phase II, double blind, randomized clinical non-inferiority trial (The Indian Polycap Study [TIPS]) evaluated the efficacy, tolerability, and safety of Polycap in over 2000 individuals in 50 centers in India. This study demonstrated that the Polycap was non-inferior to its individual components in lowering blood pressure and heart rate (a surrogate for β-blockade), but it did not reduce LDL concentrations to the same extent as simvastatin monotherapy (27 vs 32 mg/dL; $p = 0.04$) [24]. Another double-blind, randomized, placebo-controlled, cross over trial analyzed the efficacy of a polypill containing amlodipine 2.5 mg, losartan 25 mg, HCTZ 12.5 mg, and simvastatin 40 mg in 86 individuals over the age of 50 years, treated for 12 weeks followed by 12 weeks crossover to placebo [25]. Polypill therapy was associated with reductions in DBP by 9.8 mm Hg, systolic blood pressure (SBP) by 17.9 mm Hg, and LDL by 1.4 mmol/L. This would be expected to result in relative risk reductions of 72% in CVD and 64% in stroke [26]. The fact that the participants in this trial were recruited from patients already taking simvastatin and blood pressure lowering medications may have contributed to the remarkable adherence rate (98% of participants took more than 85% of their pills).

Despite some attempts with prehypertension therapy, whether BP-lowering drugs may prove beneficial in individuals without CVD, including in individuals with “normal” baseline BP levels, remains unknown.

Clinical trials have demonstrated that a combination pill was well tolerated and that it effectively reduced blood pressure and LDL-cholesterol. This resulted in a considerable reduction in the calculated risk of CVD and stroke [3]. Despite the fact that these studies seem to support the use of a low-dose polypill for the primary prevention of CVD, there are still some unresolved issues. Firstly, there are no results from long-term trials indicating actual benefits in terms of morbidity and mortality. It is likely that the ongoing TIPS-3 and prevention of Cardiovascular Disease in Middle-aged and Elderly Iranians using a single polypill (POLYIRAN) trials will be able to provide data regarding actual benefits associated with the use of the polypill in primary prevention of CVD. In the POLYIRAN trial, the effects of the polypill administration will be compared with minimal and usual care over a period of 5 years [27]. The

TIPS-3 study will compare the effects of Polycap and placebo on a composite of major CVD (CV death, non-fatal stroke, non-fatal myocardial infarction [MI]), heart failure, resuscitated cardiac arrest, or revascularization with evidence of ischemia in 5000 participants (without known heart disease or prior stroke and without a clear indication or contraindication to any of the study medications) [28]. The estimated study completion date is March 2020. Another problem of primary prevention is that asymptomatic individuals are unlikely to adhere to a lifelong regimen of medical therapy. Moreover, some consider it to be unethical to treat large portion of the population who appear to be "healthy" and "asymptomatic". Additionally, there is no convincing evidence to support the cost-effectiveness of the polypill in people with low or unknown risk factors [3]. Other concerns associated with the use of polypills in primary prevention relate to its non-specific 'scattergun' approach, which would expose people at lower risk to lifelong treatment [29].

Primary prevention is associated with numerous issues. Some evidence suggests that aspirin may exert different effect in women and men [30]. The results of the completed Women's Health Study (WHS), of low-dose aspirin (100 mg every other day) compared with placebo, demonstrated no reduction in all-cause mortality or fatal and non-fatal myocardial infarction [29].

A randomized trial of 2.5 mg/day of folic acid (the proposed polypill dosage is 0.8 mg/day) demonstrated that this was not associated with a reduction in the combined trial end point of stroke, coronary events, and death in patients with earlier cerebral infarction [31]. In contrast, in the large China Stroke Primary Prevention Trial (CSPPT) randomized clinical trial, the combined use of enalapril and folic acid considerably reduced the risk of first stroke, compared with enalapril alone. This suggests benefits from folate use among adults with hypertension and low baseline folate levels [32]. The reason why folic acid has not been demonstrated to reduce myocardial infarction may be associated with the fact that aspirin may mask the effect of folic acid due to a shared mechanism of action. Vitamin B therapy lowers plasma total homocysteine concentrations [33], however, the reduction in homocysteine level may not add to the effect of aspirin (and possibly other antiplatelet drugs) in preventing ischemic heart disease [34]. Homocysteine exerts a thrombotic effect through its action on platelet function, while aspirin irreversibly blocks the formation of thromboxane 29 in platelets, inhibiting platelet activation and platelet aggregation [35]. Due to the fact that homocysteine

exerts a thrombotic effect through its action on platelet function, concomitant treatment with aspirin could diminish or negate the antiplatelet effect of lowering homocysteine [34]. Therefore, folic acid could play a role in the primary prevention of ischemic heart disease in patients who do not take aspirin routinely, but not in secondary prevention, when aspirin is administered routinely. The hypothesis that aspirin decreases or negates the antiplatelet effect of homocysteine lowering is supported by the results of a meta-analysis that demonstrated a statistically significant difference in risk reduction between trials with the lowest and highest prevalence of concomitant antiplatelet therapy (p=0.037) [34]. Moreover, meta-analysis of three large trials: Vitamin Intervention for Stroke Prevention (VISP), VITAmins TO Prevent Stroke (VITATOPS), and Heart Outcomes Prevention Evaluation 2 (HOPE-2) revealed that in patients who were not taking antiplatelet therapy, homocysteine lowering with B-vitamins was associated with a significant reduction (29%) in overall stroke risk [36].

1. 2.3. Use of the Polypill in secondary prevention.

The use of aspirin, statins, ß-blockers, and ACE inhibitors/ARBs in the secondary prevention of CVD is beneficial. A large number of studies have demonstrated the reduction in cardiovascular-related mortality in individuals receiving appropriate medical therapy [3, 7, 37]. Multiple obstacles stand in the way of better implementation of secondary prevention strategies. Firstly, numerous studies indicate that therapies with proven efficacy are not prescribed to all who may benefit from them. According to the third European Action on Secondary Prevention Through Intervention to Reduce Events (EUROASPIRE III) survey in nine European countries, the prevalence of smoking is 17%, obesity 35%, uncontrolled BP 56%, and elevated cholesterol 25% among patients with ischemic heart disease, while the administration of statins and ACE inhibitors/ARBs is relatively low: 71% and 78%, respectively [38].

The use of appropriate drugs is even lower in developing countries. The World Health Organization study on Prevention of Recurrence of Myocardial Infarction and Stroke (WHO-PREMISE) survey was carried out in ten low- and middle-income countries and demonstrated that only 81.2% of patients with IHD and 70.6% of patients with cerebrovascular disease were prescribed aspirin, 48.1% and 22.8% β-blockers, 39.8% and 37.8% ACE inhibitors, and 29.8% and 14.1% statins [39]. The situation is worst in rural areas. A community-based

study performed in 53 villages in India revealed that only 14% patients with IHD or cerebrovascular disease were taking aspirin, 41% a BP-lowering drug, and 5% a cholesterol-lowering medication [40].

Secondly, due to numerous factors (psychological, social, cultural, economic, and clinical factors related to patients, healthcare providers, healthcare systems, and their interactions) long-term adherence to prescribed medications is poor - often <50% [7, 41]. Patient adherence to long-term therapies is among the most important public health priorities of the European Union and is a concern for the medical community [42]. Appropriate medical therapy for the secondary prevention of CVD is often associated with the need to take multiple medications. A group of patients who were administered four evidence- based medications after hospitalization for acute coronary syndrome (ACS) had considerably higher survival after 2 years than a group of patients who only received only one of these medications [43]. On the other hand, adherence has been revealed to diminish proportionally to the number of drugs taken by the patient. In patients who were hospitalized for coronary artery disease, the adherence to prescribed medications can be as low as 40% [44,45]; this may result in a 50% to 80% relative increase in the risk of mortality [46]. The polypill has the potential to resolve the problem of non-adherence to medicines used in the secondary prevention of CVD. A beneficial effect of the polypill on adherence was demonstrated in the Use of a Multidrug Pill in Reducing Cardiovascular Events (UMPIRE) study, in which medication adherence was compared in a group of patients receiving a polypill and a group receiving usual therapy. The participants had established CVD or a calculated 5-year CVD risk of >15% [47]. In this study, 2004 participants received a combination of aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg or HCTZ 12.5 mg) or usual medical therapy over 15 months. This study demonstrated that adherence was 33% better in the polypill group, and that this was associated with a reduction of SBP (2.6 mmHg) and LDL-cholesterol (4.2 mg/dL).

Finally, cost and affordability pose an important barrier, especially in low-income countries. Despite the fact that drugs used in secondary prevention are generally cost-effective, in middle- and low-income countries the cost of a 1-month supply of standard generic secondary prevention drugs ranges from 1.5 to 18.4 days' wages of government workers. Therefore some patients cannot afford the drugs they require [7,48,49]. The Prospective Urban Rural Epidemiology (PURE) study, which investigated the use of medications for secondary

prevention, in adults with a history of CVD events across countries of varying wealth demonstrated suboptimal overall use of antiplatelet drugs 25.3%, ß-blockers 17.4% and statins 14.6%) [50]. The observation that the use of appropriate medications decreased gradually with diminishing economic status was not surprising. Therefore, there is a large treatment gap between high- and low-income countries that is most clearly depicted by the difference in rates of statin use in high-income (66.5%) and low-income (3.3%) countries. Affordability is an important issue in the treatment gap. Mendis *et al*. [49] revealed that 1 month of multiple drug therapy could cost between 5.1 and 18.4 days of wages in low- and middle-income countries (LMICs). Therefore the use of a single polypill, which costs less than 50% of the sum of the prices of its components purchased separately, may improve the affordability, and in consequence improve the adherence [51]. Furthermore, the application of a Markov model demonstrated that a combination pill would be cost-effective in secondary prevention regardless of the socioeconomic level of the target population [48].

Trials indicate that fixed-dose combination therapy reduces lipid levels (using statins) and blood pressure (using angiotensin-converting enzyme inhibitors, ß-blockers and diuretics) to the same extent as giving each drug separately [52]. Also, the effects of aspirin on the suppression of markers of thromboxane 5 are similar when it is administered separately or in combination with the other components of the polypill [53].

The aim of cross-sectional Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention (FOCUS) study (Phase 1) [54] was to identify factors that interfere with appropriate adherence to CV medications for secondary prevention after an acute MI. Moreover, in the controlled trial (Phase 2) the effect of a polypill (containing aspirin 100 mg, simvastatin 40 mg, and ramipril 2.5, 5, or 10 mg) were compared with the three drugs given separately in terms of adherence, blood pressure, and low-density lipoprotein cholesterol. Safety and tolerability were also measured over a 9 months follow-up period. In the first phase of this study, overall adherence to CV medications, defined as self-reported Morisky-Green questionnaire (MAQ) score of 20, was 45.5%. Lack of adherence (MAQ <20) was associated with younger age, depression, being on a complex medication regimen, poorer health insurance coverage, and a lower level of social support. In the second phase of the study, adherence was shown to be improved in group receiving polypill in comparison to the group receiving separate medications after 9 months of follow-up: 50.8% versus 41% (p=0.019; intention-to-treat population) and

65.7% *vs.* 55.7% (p=0.012; per protocol population). In relation to treatment effects, no treatment difference was found at follow-up with respect to mean systolic blood pressure (129.6 mm Hg *vs.* 128.6 mm Hg), mean low-density lipoprotein cholesterol levels (89.9 mg/dl *vs.* 91.7 mg/dl), serious adverse events (23 *vs.* 21), or death (1, 0.3% in each group). There were no significant differences in adverse events in both groups (32% of patients in the control group vs. 35% in the polypill group; serious adverse events 6.6% in the control group vs. 6% in the polypill group) [54].

The Heart Outcomes Prevention Evaluation (HOPE)-3 trial, which assessed the concept of combined BP and cholesterol lowering in individuals without vascular disease and with average BP and cholesterol levels demonstrated that fixed-dose treatment with low-dose statin therapy, but not BP agents, is superior to placebo in reducing long-term CV events in an intermediate-risk population [55]. This trial was conducted in 256 centers in 22 countries in North and South America, Europe, Africa, Asia, and Australia and included 12,705 patients at moderate risk (men aged 55 years and women aged 65 years with one risk factor or women aged 60 years with two risk factors) The expected annual event rate in the placebo group was 0.9% to 1%. Patients were randomized to receive rosuvastatin 10 mg/d alone, a fixed-dose combination of candesartan 16 mg/hydrochlorothiazide 12.5 mg/d or rosuvastatin + candesartan + HCTZ. The fixed-dose combination of candesartan 16 mg + HCTZ 12.5 mg daily was not superior to placebo in reducing CV events despite a 6 mm decrease in SBP and a 3 mm decrease in DBP. The fixed-dose combination of all three drugs appeared to have CV benefits that were mostly similar to those observed with rosuvastatin alone [55].

The PolyIran Study [56] is an important ongoing trial assessing the effectiveness of a polypill containing hydrochlorothiazide (12.5mg), enalapril (5mg) or valsartan (40mg), atorvastatin (20mg), aspirin (81mg) in persons ≥50 years old with or without prior CVD. The primary endpoint is time to first major CV event (during a 5-year follow-up). The trial is due to be completed still in 2018. Another large trial, which will report after its completion in 2018 is the Heart Outcomes Prevention and Evaluation 4 (HOPE-4) study [57]. This open-label, parallel, cluster randomized controlled pragmatic trial is evaluating an intensive CV risk detection and control programme. The study is being carried out in Canada, Colombia, Malaysia in over 30 community clusters. The effects of a combination of blood pressure lowering medication (2-3 components) plus a statin (provided separately) will be assessed in patients ≥50 years old with

SBP ≥160 mmHg or SBP 140-159 mmHg and diagnosis of hypertension or taking anti-HTs or SBP ≥130 mmHg and diagnosis of diabetes or taking diabetes medication. Framingham Risk Score (FRS) is the primary endpoint. Finally, the Secondary Prevention of Cardiovascular Disease in the Elderly (SECURE) study [58], which is a European collaborative project funded by the EU Framework Programme for Research and Innovation, will be testing the efficacy of a fixed-dose combination (FDC) polypill Trinomia (aspirin (100mg), atorvastatin (40 or 20mg), ramipril (2.5, 5, 10mg) for secondary cardiovascular prevention in the elderly population (≥65 years old). Its main objective is to assess the potential benefit of the FDC as a component of a cost-effective, globally available and comprehensive treatment strategy for secondary prevention of cardiovascular events (death from cardiovascular causes, non-fatal myocardial infarction, stroke, and hospitalization requiring revascularization) as compared to standard therapy (the three components of the polypill given separately). Primary endpoint in this study is major adverse cardiovascular events (MACE) at 6, 12, 18 and 24 months. This study will be completed in January 2020.

1. 3. Conclusions

Recent studies have indicated that polypills are useful for the primary prevention of CVD. They act by significant reducing both BP and LDL-C concentrations. It has also been demonstrated that polypills are beneficial in secondary prevention, they improve adherence and are well tolerated. The ongoing trials: HOPE-4, OMS, PILL, SECURE, TIPS 3 and UMPIRE should help to reach a final decision concerning the safety and efficacy of the polypills.

1. 4. Expert Opinion

The results of the five studies described above, indicates that the polypill is useful for the primary prevention of CVD. It works by reducing main CVD risk factors - BP and LDL-C level [59]. Huffman *et al.* [60] performed an analysis of 13 polypill trials (9059 participants) and demonstrated that all polypills used improved adherence, were well tolerated, and reduced risk factor levels. These benefits have been observed in both primary and secondary prevention.

As indicated, the polypill may have several advantages. First, it enables the avoidance of complex treatment algorithms to identify individuals for therapy. It increases the ease of

prescribing and eliminates the need for dose titration of each drug [7]. This advantage remains unproven, however, a study of high-risk patients with IHD and/or diabetes mellitus receiving a "cardioprotective bundle" demonstrated that the simplified regimen (fixed doses, minimal physician visits, laboratory tests, and dose titration) led to diminished risk of hospitalizations for IHD or stroke within 1 year [61].

The use of polypill may enhance adherence due to the fact that patient is taking one tablet or capsule instead of several. In patients receiving medicines for the secondary prevention of CV prevention patients, compliance decreases over time. This has an important impact on health, morbidity and healthcare costs [62]. The results of a *post-hoc* analysis of the SPACE Collaboration data set suggests that the adherence benefits of polypills will outweigh the loss of potency associated with the use of low doses of the individual components [63]. The effectiveness of the combined use of two antihypertensive agents (ARB and diuretic) at a half dose and statin in the primary prevention of CVD in individuals with intermediate risk and without CVD was confirmed in the recent HOPE-3 study [62,64]. Not all patients with CV problems are administered all recommended drugs. Therefore, administration of a polypill containing all necessary components (even in reduced doses) may be associated with benefits. Finally, the low dose of the component drugs in polypills may be associated with a lower frequency of side effects. This benefit may outweigh the loss of potency. In the case of statin-therapy, this may be especially important. Real and perceived adverse effects of statin therapy lead to discontinuation of therapy with consequent poor outcomes. This phenomenon of 'statin intolerance' can be managed in many cases with lower doses of statin (or alternate day dosing), whilst retaining lipid lowering efficacy to a large extent [65,66]. A low-dose of statin in a polypill is therefore likely to lower CV risk bur minimise adverse effects. However, in the case of primary prevention, subjects who feel healthy may not be motivated to use medications for a long time. Therefore, even minor side effects to one component of the polypill may result in its discontinuation and the loss of benefit from all component drugs.

The cost-effectiveness of polypills in comparison to separate administration of the individual components has been demonstrated in various populations. According to estimates, the costs of a polypill containing generic components is ~$1 a day in developed and 20 cents in developing countries, which is much lower than the costs of individual drugs [7]. Cost-reduction may be associated with reduced expenditures on packaging, distribution, and lower marketing

costs as well as fewer physician visits and laboratory tests. One study designed to estimate the health benefits and cost-effectiveness of a polypill intervention (aspirin 100 mg, atorvastatin 20 mg, ramipril 10 mg) compared with multiple monotherapy for secondary prevention of cardiovascular events in adults with a history of myocardial infarction demonstrated that over a 10-year period, the use of the cardiovascular polypill would avoid 46 non-fatal and 11 fatal cardiovascular events per 1000 patients treated [42]. However, the real cost of a polypill will not be known before a product gains marketing authorization. It will depend on the costs of the "raw ingredients" and packaging but will also include costs of product formulation, research and development, registration, marketing and distribution, as well as "profit" for manufacturers [7].

Healthcare regulators are implementing unnecessary barriers to the licensing of polypills when the individual components are already licensed products. In general, no clearly defined pathway to regulatory approval is available apart from a 'straight substitution' indication based on bioequivalence data [67]. The requirement to conduct additional tests and randomized clinical trials not only delays the introduction of new treatments, but also increases costs. Recently the FDA set up a Combination Products Policy council aiming at establishing unified requirement for approving combination therapies. This approach seems to be a step in a right direction [67].

The implementation of the polypill is also limited due to the existence of patents for its components. In Canada and the United States, the availability of off-patent cardiovascular medication was estimated to be only 40% [68]. The potential usefulness of a polypill may be also reduced due to an ongoing preference for tailored treatment, resulting in a reluctance of health care providers to prescribe polypills. However, evidence indicates that more and more physicians are recognizing the potential benefits of the polypill, which improves adherence and can be successfully used in the secondary prevention of CVD [67]. Another issue for health care providers is the lack of universal guidelines supporting the use of polypills [67]. The absence of a generally available polypill, nearly 20 years after the concept was proposed, represents a failure of the medical community to grasp an enormous opportunity to prevent disease.

However, the composition of the "ideal" polypill remains to be confirmed. There are many unanswered questions. Are the ingredients of the polypill sufficient to achieve anticipated effects in primary and secondary protection? Is there a need to add some new element or to modify the old ones? Should the pill contain aspirin which has a negligible role in primary prevention and which increases the risk of gastrointestinal bleeding and the risk of allergy? The

Medicines and Health Products Regulatory Agency has decided that it is reasonable to avoid using ACE-inhibitor in polypill due to its side effects. An Angiotensin receptor blocker (losartan) seems to be a better choice since it exerts similar blood pressure lowering effect as an ACE-inhibitor and rarely causes a cough [69]. The debate over the use of aspirin in polypills is still open. Aspirin is undoubtedly effective in secondary prevention, however, its benefits may be very limited in primary prevention when the absolute risk is low due to the cholesterol and blood pressure reduction achieved by the use of other components of the polypill. It is also unclear whether the benefits of aspirin outweigh the harms [69]. Recent finding that aspirin may protect against cancer may tip the scales in favor of aspirin.

The polypill may not be suitable for all who wish to benefit from it. Consideration should be given to producing a small range of polypills to make them as widely available as possible [70,71]. For example, a polypill without a β-blocker for would be useful in persons with asthma. A polypill with an increased dose of statin may be useful for those in whom very low LDL-cholesterol levels are desirable [7]. Moreover, patients at extremely high risk (e.g., those with very aggressive manifestations of atherothrombotic disease) as well as those with side effects to multiple medications may still require individualized therapy. The introduction of many polypills would further complicate the situation and therefore it seems that the use of two polypills for primary and secondary prevention (including aspirin and a beta-blocker) may be reasonable.

On 23rd May 2016, the 2016 European Guidelines on cardiovascular disease prevention in clinical practice by the European Society of Cardiology (ESC), advised that the polypill could be considered as a treatment option, as part of a comprehensive CVD prevention strategy in certain patients [72].

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One referee declares that they are the founder of Polypill Ltd.

ARTICLE HIGHLIGHTS BOX

- The polypill has been shown to be effective in the primary prevention of cardiovascular disease (CVD).
- The polypill makes prescribing easier by reducing the need for complex treatment algorithms and dose titration.
- The use of polypills may enhance adherence by simplifying the dosing regimen. The adherence benefits of polypills outweigh the loss of effectiveness associated with the use of low doses of individual components.
- There are still many issues that need to be addressed before the polypill can be routinely used. There is no clearly defined pathway to regulatory approval.
- Healthcare Regulators are imposing unnecessary barriers to the licensing of polypills. Furthermore, the implementation of the polypill is made difficult by the existence of patents for its component drugs. The composition of "ideal" polypill remains to be confirmed.
- On May 2016, the European Guidelines on cardiovascular disease prevention in clinical practice by the European Society of Cardiology advised that the polypill could be considered as a treatment option in certain patients., as part of a comprehensive CVD prevention strategy.

REFERENCES:

1. World Health Statistics. 2011. Cardiovascular diseases (CVDs) fact sheet. Available at: http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed on 20.03.2018

2. Mendis S, Puska P, Norrving B. Global Atlas on Cardiovascular Disease Prevention and Control. Geneva, Switzerland: World Health Organization; 2004.

3. Wiley B, Fuster V. The Concept of the Polypill in the Prevention of Cardiovascular Disease. Annals of Global Health 2014;80:24-34

4. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case control study. Lancet. 2004;364:937e52

**5. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003;326:1419.

(the first publication on polypill)

6. Castellano JM, Sanz G, Fernandez Ortiz A, et al. A Polypill Strategy to Improve Global Secondary Cardiovascular Prevention From Concept to Reality* J Am Coll Cardiol 2014;64:613–21

7. Lonn E, Bosch J, Teo KK, et al. The Polypill in the Prevention of Cardiovascular Diseases Key Concepts, Current Status, Challenges, and Future Directions. Circulation. 2010;122(20):2078-88.

8. Clarke R, Halsey J, Lewington S, et al. for the B-Vitamin Treatment Trialists' Collaboration. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: meta-analysis of 8 randomized trials involving 37,485 individuals. Arch Intern Med. 2010;170:1622–1631.

9. Baigent C, Blackwell L, Collins R, et al. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373:1849–1860.

10. McNeil JJ, Wolfe R, Woods RL et al. ASPREE Investigator Group. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. N Engl J Med. doi: 10.1056/NEJMoa1805819

11. Gaziano JM, Brotons C, Coppolecchia R, et al. ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet. 2018 doi: 10.1016/S0140-6736(18)31924-X

12. ASCEND Study Collaborative Group. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med. 2018 doi: 10.1056/NEJMoa1804988.

13. Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. Lancet. 2018 Aug 4;392(10145):387-399.

14. Kearney PM, Blackwell L, Collins R, et al. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371:117–125.

15. Armitage J. The safety of statins in clinical practice. Lancet. 2007;370:1781–1790

16. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375:735–742

17. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low-density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003;326:1423e9.

18. Law MR, Wald NJ, Moris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ. 2003;326:1427–1431

19. Patel A, Shah T, Shah G, et al. Preservation of bioavailability of ingredients and lack of drug-drug interactions in a novel five-ingredient polypill (Polycap). Am J Cardiovasc Drugs. 2010; 10: 95–103

20. Ebrahim S, Beswick A, Burke M, Davey SG. Multiple risk factor interventions for primary prevention of coronary heart disease. Cochrane Database Syst Rev. 2006;4:CD001561.

21. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. BMJ. 2002;324:1570–1577.

22. Teo KK, Ounpuu S, Hawken S, et al. INTERHEART Study Investigators. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. Lancet. 2006;368:647–658.

23. Lewington S, Clarke R, Qizilbash N, et al. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–1913.

**24. The Indian Polycap Study. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. Lancet. 2009; 373: 1341–1351

(presents results of polypill use in a randomized trial)

**25. PILL Collaborative Group, Rodgers A, Patel A, Berwanger O, et al. An international randomised placebo-controlled trial of four-component combination pill ("polypill") in people with raised cardiovascular risk. PLoS One. 2011; 6: e19857

(presents results of polypill use in a randomized trial)

26. Wald DS, Morris JK, Wald NJ. Randomized polypill crossover trial in people aged 50 and over. PLoS One. 2012; 7: e41297

**27. Tehran University of Medical Sciences. Prevention of Cardiovascular Disease in Middle-aged and Elderly Iranians Using a Single PolyPill (PolyIran).In: ClinicalTrials.gov [Internet].Available from: http://clinicaltrials.gov/ct2/show/NCT01271985. Accessed March 12, 2018.

(presents results of polypill use in a trial)

**28. Population Health Research Institute;The International Polycap Study 3 (TIPS-3). In: ClinicalTrials.gov [Internet]. Available from: http://clinicaltrials.gov/ct2/show/study/NCT01646437 Accessed March 12, 2018.

(presents results of polypill use in a trial)

**29. Ridker PM, Cook N, Lee I, et al. A randomised trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352: 1293-304.

(presents results of polypill use in a randomized trial)

30. Fahey T, Brindle P, Ebrahim S. The polypill and cardiovascular disease: May be appropriate for secondary, but perhaps not for primary prevention. BMJ: British Medical Journal 2005;330(7499):1035-1036.

31. Toole J, Malinow MCL, Spence J, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction and death. The vitamin intervention for stroke prevention (VISP) randomized controlled trial. JAMA 2004;291: 565-75

32. Huo Y, Li J, Qin X, et al. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. JAMA. 2015 Apr 7;313(13):1325-35.

33. Spence JD, Yi Q, Hankey GJ. B-vitamins in stroke prevention: time to reconsider. Lancet Neurol. 2017;16(9):750-760.

34. Wald DS, Morris JK, Wald NJ (2011) Reconciling the Evidence on Serum Homocysteine and Ischaemic Heart Disease: A Meta-Analysis. PLoS ONE 6(2): e16473

35. Vane JR, Botting RM. The mechanism of action of aspirin. Thromb Res 2003;110: 255–8

36. Park JH, Saposnik G, Ovbiagele B, Markovic D, Towfighi A Effect of B-vitamins on stroke risk among individuals with vascular disease who are not on antiplatelets: A meta-analysis. Int J

Stroke. 2016 Feb;11(2):206-11

37. Ford EA, Ajani UA, Croft JB, et al. Explaining the decline in coronary mortality in the United States between 1980 and 2000. N Engl J Med. 2007; 356: 2388–2398

38. Kotseva K, Wood D, De Backer G, et al. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. Eur J CardiovascPrevRehabil. 2009; 16: 121–137

39. Mendis S, Abegunde D, Yusuf S, et al. WHO study on Prevention of Recurrences of Myocardial Infarction and Stroke (WHOPREMISE). Bull World Health Organ. 2005;83:820–829

40. Joshi R, Chow CK, Raju PK, et al. Fatal and non-fatal cardiovascular disease and the use of therapies for secondary prevention in a rural region of India. Circulation. 2009;119:1950–1955

41. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487–497.

*42. Barrios V, Kaskens L, Castellano JM, et al. Usefulness of a Cardiovascular Polypill in the Treatment of Secondary Prevention Patients in Spain: A Cost-effectiveness Study. Rev EspCardiol (Engl Ed). 2017;70(1):42-49

(study presenting economic analysis of polypill use)

43. Lahoud R, Howe M, Krishnan SM, et al. Effect of use of combination evidence-based medical therapy after acute coronary syndromes on long-term outcomes. Am J Cardiol. 2012; 109: 159–164

44. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA. 2002; 288: 462–467

45. Newby LK, LaPointe NMA, Chen AY, et al. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. Circulation. 2006; 113: 203–212

46. Ho PM, Magid DJ, Shetterly SM, et al. Medication non-adherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. Am Heart J. 2008; 155: 772–779

47. Thom SA. Use of a Multidrug Pill in Reducing Cardiovascular Events (UMPIRE). Paper presented at: AHA Scientific Sessions. November 5, 2012. Los Angeles, California.

48. Gaziano TA, Opie LH, Weinstein MC. Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. Lancet. 2006; 368: 679–686

49. Mendis S, Fukino K, Cameron A, et al. The availability and affordability of selected essential

medicines for chronic diseases in six low- and middle-income countries. Bull World Health Organ. 2007; 85: 279–288

50. Yusuf S, Islam S, Chow CK, et al. 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: 1231–1243

51. Sanz G,Fuster V. Polypill and global cardiovascular health strategies. Semin Thoracic Surgery. 2011; 23: 24–29

52. Huffman MD, Yusuf S. Polypills. Essential Medicines for Cardiovascular Disease Secondary Prevention? J Am CollCardiol 2014;63:1368–70

53. Elley CR, Gupta AK, Webster R, et al. The efficacy and tolerability of 'polypills': meta-analysis of randomised controlled trials PLoS One 2012;7:e51245

54. Castellano JM, Sanz G, Peñalvo JL, et al. A Polypill Strategy to Improve Adherence Results From the FOCUS Project. J Am CollCardiol 2014;64:2071–82

55. Yusuf S, Bosch J, Dagenais G, et al; HOPE-3 Investigators. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med. 2016;374(21):2021-31.

**56. Tehran University of Medical Sciences, Prevention of Cardiovascular Disease Using a Single PolyPill in an Urban Population - Focus on Liver-Related Variables. (PolyIran-L)In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://clinicaltrials.gov/ct2/show/NCT01245608; Accessed: 12 March 2018

(presents results of polypill use in a trial)

**57. Hamilton Health Sciences Corporation. Heart Outcomes Prevention and Evaluation 4 (HOPE-4). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://clinicaltrials.gov/ct2/show/NCT01826019; Accessed: 12 March 2018

58. http://www.secure-h2020.eu/ Accessed: 12 March 2018

(presents results of polypill use in a clinical trial)

59. Chrysant SG, Chrysant GS. Usefulness of the polypill for the prevention of cardiovascular disease and hypertension. Current Hypertension Reports 2016; 18: 14

**60. Huffman MD, Xavier D, Perel P. Uses of polypills for cardiovascular disease and evidence to date. Lancet 2017; 389: 1055–1065

(analysis of 13 polypill trials)

61. Dudl RJ, Wang MC, Wong M, Bellows. Preventing myocardial infarction and stroke with a simplified bundle of cardioprotective medications. Am J Manag Care. 2009;15:e88–e94.
62. López-Jaramillo P, González-Gómez S, Zarate-Bernal D, et al. Polypill: an affordable strategy for cardiovascular disease prevention in low-medium-income countries. Ther Adv Cardiovasc Dis. 2018;12(6):169-174
63. Webster R, Bullen C, Patel A, Selak V, Stepien S, Thom S, Rodgers A. Impact of switching to polypill based therapy by baseline potency of medication: Post-hoc analysis of the SPACE Collaboration dataset. Int J Cardiol. 2017;249:443-447
64. Lonn E, Bosch J, Pogue J, et al. Novel approaches in primary cardiovascular disease prevention: The HOPE-3 trial rationale, design, and participants' baseline characteristics. Can J Cardiol 2016; 32: 311–318
65. Banach M, Mikhailidis DP. Statin Intolerance: Some Practical Hints. Cardiol Clin. 2018 May;36(2):225-231.
66. Awad K, Mikhailidis DP, Toth PP, et al. Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Efficacy and Safety of Alternate-DayVersus Daily Dosing of Statins: a Systematic Review and Meta-Analysis. Cardiovasc Drugs Ther. 2017 Aug;31(4):419-431.
67. Brimble, M, Tay, D, Pears, J. Cardiovascular polypill. Current and evolving landscape for primary and secondary prevention, https://wellcome.ac.uk/sites/default/files/cardiovascular-polypill-feb17.pdf (2016, accessed 25 July 2017)
68. Beall RF, Schwalm J-DR, Huffman MD, et al. Could patents interfere with the development of a cardiovascular polypill? J Transl Med 2016; 14: 242.
69. Wilkinson E. A look at the polypill story 10 years later. Interest in the polypill continues with an on-going study in the UK. Eur Heart J 2013; 34, 2019–2024
70. Lopatowska P, Mlodawska E, Tomaszuk-Kazberuk A, et al. Adhering to the principles of clinical pharmacology - the correct fixed combinations of antihypertensive drugs. Expert Rev Clin Pharmacol. 2018;11(2):165-170.
71. Kolte D, Aronow WS, Banach M. Polypills for the prevention of Cardiovascular diseases. Expert Opin Investig Drugs. 2016;25(11):1255-1264.
72. Piepoli MF, Hoes AW, Agewall S, et al; ESC Scientific Document Group. 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(29):2315-2381.