CLINICAL INVESTIGATION

Polypill (fixed-dose combination) in the prevention of cardiovascular disease: rationale and clinical data

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Cardiovascular diseases (CVDs) continue to be major contributors of death and disability globally. Control of CVD risk factors has been shown to be effective in reducing morbidity and mortality both in primary and secondary prevention settings. Given the cumulative benefits of concurrently controlling multiple CVD risk factors (high blood pressure, dyslipidemia and platelet activity) in individuals at high risk, administration of a polypill consisting of antihypertensive, antidyslipidemic and antiplatelet agents together could simultaneously lower multiple risk factors and applying such a population risk-reduction strategy has the potential to considerably reduce CVD burden. Furthermore, the availability of an inexpensive generic polypill might improve medication adherence and reduce the evidence–practice gap for individuals who already have an indication for long-term treatment with these agents. A few clinical trials have provided early evidence about the safety and efficacy of polypill in primary prevention, however, the result of studies with hard clinical outcomes is some years away.

Keywords: aspirin • blood pressure-lowering agents • cardiovascular disease • fixed-dose combination therapy • hyperlipidemia • hypertension • multidrug pill • polypill • statins

Kavita Singh[1], Abdul Salam[2], Raji Devarajan[3], Anushka Patel[4] & Dorairaj Prabhakaran*[1,3]

[1]Center for Chronic Disease Control (CCDC), New Delhi, India
[2]The George Institute for Global Health, Hyderabad, Andhra Pradesh, India
[3]COE-CARRS, Public Health Foundation of India (PHFI), New Delhi, India
[4]The George Institute for Global Health, Sydney, Australia
*Author for correspondence:
Tel.: +91 11 4342 1957
Fax: +91 11 4342 1975
E-mail: dprabhakaran@ccdcindia.org

Cardiovascular diseases (CVDs) are the major contributors of deaths and disability worldwide and are projected to increase in prevalence if the current trend continues [1]. An estimated 17.3 million people died from CVDs in 2008, representing 30% of all global deaths. By 2030, this figure is expected to increase to 23.3 million CVD-related deaths. The majority of these deaths (>80%) now occur in low- and middle-income countries (LMICs), in relatively young populations compared with western counterparts [2,3]. There is a strong rationale to expect that both effective population-wide primary prevention and individual healthcare approaches will be required to reduce the burgeoning population burden of CVDs [4].

An array of interventions ranging from primordial prevention strategies such as promoting physical activity and healthy lifestyle and diet, to use of low-cost preventive drugs for controlling blood pressure (BP), to relatively costly interventions, such as percutaneous coronary interventions or coronary artery bypass graft surgery are available for CVD management [5]. Although randomized trials have shown statins and BP lowering drugs to be useful in primary prevention, the benefits of aspirin in this context remains controversial [6–11]. On the one hand, there is substantial evidence to support the clear benefits of aspirin, statins and BP lowering drugs in secondary prevention of CVD [12–15]. However, "suboptimal management of CVDs in most countries impose a considerable healthcare challenge" [16]. For example, the PURE study showed poor utilization of cardiovascular (CV) medications. In this study the self reported

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use of essential CV drugs (statins, BP-lowering and antiplatelet agents) was less than 25 and 10% among individuals with established CVD in developed and developing countries, respectively [17,18].

Guidelines for the management of CVD emphasize treating global risk [201], which is supported by the results of prospective cohort studies, wherein patients at high CVD risk have shown to largely benefit from a combination therapy of aspirin, BP-lowering and lipid-lowering agents [19,20]. However, it is likely that increasing the number of drugs may decrease patients' adherence to these CV preventive treatments. Poor adherence to multidrug regimens is a common barrier to effective therapy [21]. In the LMIC, unaffordable costs of such regimens represent another obstacle [22]. Combination pharmacotherapy, in the form of CV polypill or fixed-dose combinations (FDC), offer potential to decrease the incidence of CVD worldwide by addressing the issues of affordability and complexity of multidrug regime; however, the role of such a polypill in the prevention of CVD has been debated extensively over the last decade [23–25,202]. To date, only a couple of studies have investigated polypill in primary prevention and a handful of studies are underway investigating the role of polypill in improving adherence to indicated treatments for secondary prevention of CVD.

In this article, we review the rationale behind polypill strategy in the prevention and treatment of CVDs and present the available clinical data.

Rationale for polypill (FDC) concept

Polypill concept & its history

Aspirin, ACE inhibitors, beta blockers and lipid-lowering agents lower the risk of CV events, by approximately 15–25% each [24]. It has been hypothesized that although these drugs are largely proven to be efficacious independently, when prescribed together their effects remain independent such that they may reduce the risk of future CVD events by well over 50%. A combination pill for the prevention of CVD was first described in 2000 and the term 'polypill' was coined [101,102]. In an expert panel meeting in 2001 convened by the WHO and the Wellcome Trust, the potential of affordable interventions including FDC pills for noncommunicable diseases was discussed, recognising that a single pill may not only improve adherence but may also be cost-effective [26]. This theoretical concept of combination pill for CVD prevention was further expounded by Yusuf in 2002 [24] and subsequently in 2003 the first full exposition of the scientific evidence for CV combination pills (polypill) was published in the *BMJ*, from where the polypill concept gained widespread attention [23]. Wald and Law projected the cumulative benefits of combining six medications, (a statins, three BP-lowering agents, an antiplatelet agent and folic acid) based on meta-analysis results of previously published randomized trials of these drugs in CVD prevention. Their modelling estimates demonstrated that such a polypill has the potential to reduce cardiovascular events by over 80% and the authors proposed use of polypill in any individual above the age of 55 years without even quantifying the CV risk factors (based on age being the predominant driver of CVD risk). Furthermore, Wald and Law optimistically articulated that, "*The polypill has the potential to be a daily preventive method against heart attacks and strokes, just as the contraceptive pill is a daily preventive method to avoid an unwanted pregnancy*" [101,102].

Rationale behind selection of drugs for CV polypill (FDC)

The selection of individual components, doses, formulation type and regulatory issues present unique challenges in the pharmaceutical development of a CV polypill. A positive linear relationship has been seen between the number of active components in polypill and the rise in technical problems of formulation development along with likely increase in drug interactions. Therefore, a FDC pill needs to balance between pharmacological galenic (galenic formulation deals with the principles of preparing and compounding medicines in order to optimize their absorption, which has an impact on pharmacokinetics, pharmacodynamics and safety profile of a drug) challenges and its clinical usefulness. In compliance to guidelines for CVD management, agents such as aspirin, statins, ACE inhibitors and beta blockers are recommended in all patients after an acute myocardial infarction and/or stroke who do not have any contraindications to these drugs. Therefore, these agents are considered as potential components of polypill or FDC designed for secondary prevention of CVD.

Antiplatelet agents

Results of meta-analysis from the Antithrombotic Trialist Collaboration group have demonstrated that aspirin treatment significantly reduces the incidence of new CVD events – for every 1000 patients treated with antiplatelet agents, 18 nonfatal reinfarctions, 14 vascular deaths and five non-fatal strokes are prevented [27]. However, no significant differences were seen in efficacy between the high (500–1500 mg) and low dose of aspirin (75–325 mg), with corresponding vascular events rates being 14.1 versus 14.5%. Therefore, based on the A level of evidence in the American Heart Association and American College

of Cardiology guidelines, aspirin is recommended as a key component for secondary prevention of CVD and should or can be included in the FDC pill [28]. However the role of aspirin in primary prevention remains unclear as evidenced by the contradictory reports of the US and UK studies (Physicians Health Study, British Doctors Trial) [29,30].

BP-lowering agents

Several reports have shown that levels of BP linearly correlate with the risk of coronary heart disease (CHD) and stroke [31,32]. A meta-analysis published in 2006 by Dagenais *et al.* involving 30,000 patients (half with a history of myocardial infarction [MI]), ACE inhibitors demonstrated a statistically significant reduction in all cause mortality by 14% [33]. In a subgroup analysis using data from the same study, efficacy of ACE inhibitors was maintained, even when given in addition to other antiplatelet and lipid-lowering medications, which reflects an important consideration in the development of FDC therapies. Benefits from long-term therapy with beta blockers in patients with established CHD are well proven and has shown to reduce all-cause mortality by 20–34% [34]. Furthermore no significant differences in efficacy have been seen among different classes of beta blockers (atenolol, metoprolol, propoanolol, timolol and so forth). Although the potential side effects are several, these do not necessitate discontinuation of treatment in most instances. Since dose titration is viewed as an important method to avoid side effects, inclusion of beta blockers in a FDC pill might present a unique challenge to its formulation.

Lipid-lowering agents

Recent meta-analysis results from the prospective studies collaboration group published in 2007, involving data on 55,000 vascular deaths, have shown positive association between levels of total cholesterol and CVD deaths [35]. An earlier meta-analysis published in 2003 by Law *et al.* demonstrated that a reduction in LDL-cholesterol (LDL-C) by 1.5 mmol/l resulted in 20–50% reduction in CVD events [36]. Therefore, based on the strong evidence on clinical efficacy of statins, it should/can be included in the FDC pill for primary and secondary prevention of CVD events.

In the absence of clinical trial evidence confirming the added benefits of folic acid [37–39] into a combination pill for CVD prevention that already contains aspirin, statins and two BP-lowering drugs, some authors have suggested combinations of four drugs that may be customized separately for primary and secondary prevention of CHD and stroke [22]. Recent trial evidence has been cited in support of the recommendation that primary prevention regimens should include a calcium-channel blocker, whereas secondary prevention regimens must include a beta blocker [40]. ACE inhibitor and statins would potentially be incorporated in both types of regimens.

■ Potential benefits of polypill-based treatment strategy

The overall estimate for effect attributable to appropriate combination drug treatment in secondary prevention is a 55% reduction of absolute risks of major clinical events over 5 years (increasing over time, as benefits of BP and cholesterol lowering take 1–2 years to evolve) and the predicted side-effects are low (0.6% equates to six per 1000 people over 5 years) as determined from randomized trials [23,24]. Therefore, potential large benefits are possible, with few side effects using polypill-based treatment strategy.

Furthermore, almost half of all CV events (heart attack and stroke) occur in people who can be fairly readily identified as being at high risk and preventing progression of their CVD can be optimised by addressing major risk factors. Promotion of a healthy lifestyle is important but pharmacological approaches take precedence for secondary prevention.

Adherence

Among individuals with established CVD, multiple medications are required to manage CVD and it is well established that some people adhere to prescribed treatments and others do not. Discontinuation of CV-preventive medications and low adherence rates has been well documented and shown to affect the success of CVD prevention efforts.

The poor adherence to treatment is often under recognized as it is not directly assessed by physicians. Of the 45 million patients treated with BP and lipid-lowering agents in the USA, approximately 40% did not adhere to treatment [203]. Another survey in USA has shown that patients' beliefs, medication cost, lack of understanding of their condition or medication, and perception of the value of their therapy are important patient factors that promote nonadherence. Participants indicated that nonadherence occurs more frequently among minority and elderly patients, and less frequently when a caregiver is involved [41]. Patients' compliance to CV drugs is also likely to be adversely affected by a number of other factors including complexity of medication regime (i.e., numbers of tablets and multiple dosages), and associated clinic-visits cost borne by both healthcare providers and patients [42,43]. Cost of medications is a particularly important contributor in the complex phenomenon of nonadherence to medications,

where studies have shown that patients often delay or miss doses and do not refill their prescription as strategies to reduce cost [44,45]. It is therefore a reasonable hypothesis that reducing the number of pills and possibly reducing cost of medications would increase adherence to therapy [46]. There is some, however limited, evidence of improved medication compliance when FDC treatments are used in the management of a variety of conditions for example as shown in the observational studies of hypertension and hyperlipidemia management [46].

Medication adherence that is measured at the patient level, captures the combined effect of changes by both the healthcare provider (appropriate prescription) and the patient (adherence to indicated therapy). Considerable difficulties have been reported in reliably measuring patient-level adherence by self-reported questionnaire method [47]. Use of self report or pill counts can result in significant misclassification of patient adherence. On the contrary, more sophisticated methods, such as electronic monitoring of pill bottle caps, are costly and of uncertain reliability. A complementary approach is to use biological markers (i.e., levels of BP and cholesterol) that directly reflect the meaningful consequences of changes in adherence, which are more reliably quantified and translate directly to improvements in hard clinical outcomes. More recently, some researchers have suggested a mixed method approach to reliably understand the barriers to medications adherence, wherein qualitative studies (e.g., in-depth patient interviews) are combined with tools such as discrete choice experiments (which estimate patients stated preferences) to determine the actual factors that influence adherence to therapy [48].

Public health policies to reduce the escalating burden of CVD can only be effective if they recognize and address the barriers to medication adherence [21]. Additionally, at a health-system level there is a clear need to improve adherence to indicated treatments in people at greatest risk of CV events, primarily because significant disparities in guideline-based CVD treatment and current practice exist for CVD prevention across all health economies [49,50]. Barriers to the uptake of recommended guidelines by the physicians may include time constraints, multiplicity of national and several international guidelines, lack of awareness and inadequate resources to implement recommended guidelines in daily clinical practice [21]. Other key factors contributing to evidence–practice gaps may include inequities in health services, stigmatization of prescribing more than four CV medicines and lower follow-up rates by the patients [51]. It is possible that by using low-cost simplified drug regimen (perhaps polypill [FDC]) rather than conventional multiple pills prescribed for CVD prevention, will not only improve adherence (physicians, patients and guidelines), but may also reduce medication errors.

Cost–effectiveness

A recent report by Lim *et al.* estimated the number of deaths that could be averted and the financial cost of scaling up a multidrug regimen (comprising a statins, aspirin, and two BP-lowering medicines) for prevention of CVD in 23 LMICs. The authors concluded that over a 10-year period, scaling up of this multidrug regimen could avert 17.9 million deaths from CVD (95% CI: 7.4–25.7 million). In total 56% of deaths averted would be in those younger than 70 years, with more deaths averted in women than in men owing to larger absolute numbers of women at older ages. The average cost per treated individual per year is US$55 and the 10-year financial cost of this multidrug regimen would be $47 billion ($33–61 billion) or this can be translated into an average yearly cost per head of $1.08 ($0.75–1.40) across LMICs, as an investment plan for scaling up of multidrug regimen for CVD prevention [52].

Based on the experiences of using FDC pills in HIV, tuberculosis and malaria treatment, it is implicated that a polypill formulation using generics will be inexpensive and its lower cost could be attributed to mass savings in packaging, handling, distribution, prescription and fewer physician visits. Furthermore, a polypill may lead to improved access and equity if it is administered through existing non-physician healthcare workers. All of this may translate into a huge impact globally in CVD prevention, while it is equally imperative to focus on the 'causes of the causes' as elucidated by Geoffrey Rose in 1992, "Mass diseases and mass exposures require mass remedies." Hence, population-wide strategies are important in primary prevention [53].

In LMICs such as India, there is an even greater rationale for exploring the possibilities of simplified CVD prevention regimes such as polypill. These countries are at a point on the CV epidemic curve where mortality and morbidity is still rising steeply. Many parts of the population can not only be completely excluded from effective treatment, but others are incurring treatment costs far higher than those found in high income countries and being grossly impoverished in the process [54]. Therefore, given that >80% of CVD burden afflicts developing countries with scarce resources to efficiently tackle them; a priority in the LMIC region is to deliver affordable and accessible treatments and healthcare

Table 1. Main characteristics of studies of polypill in primary prevention of cardiovascular disease.

	TIPS [55]	Malekzadeh *et al.* [56]	PILL [57]	WHO study [58]	Wald *et al.* [59]
Author (Sponsor)	Yusuf *et al.* (Cadila Pharmaceuticals)	Malekzadeh *et al.* (Tehran University of Medical Sciences Research Funds)	Rodgers *et al.* (Wellcome trust)	Soliman *et al.* (WHO)	Wald *et al.* (Barts and the London Charity)
Trial registration	NCT00443794	ISRCTN43076122	ACTRN12607000099426	NCT00567307	ISRCTN36672232
Recruitment location	India	Iran	Australia, Brazil, India, Netherlands, UK, USA	Sri Lanka	London
Recruitment period	March 2007–August 2008	July 2006 and January 2007	October 2008–December 2009	February 2009–July 2009	December 2010 and March 2011
Target sample size (n)	2000	504	400	200	80
Participants randomized (n)	2053	475	378	216	86
Main inclusion criteria	Age ≥ 45 ≤ 80 Y, 1 ≥ CVD risk factor(s), no H/O CVD	Age 50–79 Y-M or 55–79 Y-F, no H/O CVD	Age >18 Y, 5-Y CVD risk ≥7.5% or 5–7.5% + 2≥ risk factors (Framingham score), no H/O CVD	Age F ≥ 50 Y and M ≥ 40 Y, 10-Y CVD risk ≥ 20% (WHO score), no H/O CVD	M/F Age ≥ 50, taking simvastatin and BP-lowering drugs, no H/O CVD
Intervention	Aspirin 100, ramipril 5, HCTZ 12.5, atenolol 50, simvastatin 20 mg	Aspirin 75, lisinopril 10, HCTZ 12.5, simvastatin 20 mg	Aspirin 75, lisinopril 10, HCTZ 12.5, simvastatin 20 mg	Aspirin 75, lisinopril 10, HCTZ 12.5, simvastatin 20 mg	Amlodipine 2.5, losartan 25, HCTZ 12.5, simvastatin 40 mg
Polypill manufacturer	Cadila	ADCT	DRL	DRL	Cipla
Comparator	Eight treatment groups: aspirin alone, simvastatin alone, HCTZ alone, T+R, T+A, R+A, T+R+A, T+R+A+aspririn	Placebo	Placebo	Standard care	Placebo
Follow up (months)	3	12	3	3	3 (12 + 12 weeks) crossover trial
Primary outcomes	LDL-C, SBP, DBP, HR, 11-dTXB2, polypill discontinuation	LDL-C, SBP, DBP	LDL-C, SBP, polypill tolerability	SBP, T-C, 10-Y CVD risk	LDL-C, T-C, SBP, DBP
Secondary outcomes	–	T-C, TGs, HDL-C, FG, major CVD events, adverse reactions	Treatment adherence, DBP, HDL-C, T-C:HDL-C ratio, non-HDL-C, TGs, frequency of switching/adding open-label treatment	Physician and patient acceptability of the polypill	Adverse effects, adherence

11-dTXB2: 11-dehydrothromboxaneB2; A: Atenolol; ADCT: Alborz Daru Company Tehran; BP: Blood pressure; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; DRL: Dr Reddy's Laboratories; F: Female; FG: Fasting glucose; H/O: History of; HCTZ: Hydrochlorothiazide; HDL-C: HDL-cholesterol; HR: Heart rate; LDL-C: LDL-cholesterol; M: Male; R: Ramipril; SBP: Systolic blood pressure; T: Thiazide; T-C: Total cholesterol; TGs: Triglycerides; Y: years.

delivery strategies. A low-cost polypill is feasible by combining off-patent generic components of aspirin, statins and BP-lowering agents. Such a combination pill strategy may produce substantial clinical and public health gains by ensuring that patients worldwide receive evidence-based CV preventive treatments.

Clinical trials of the polypill in primary prevention of CVD

Since the development of the polypill strategy in the last decade, five studies have reported the effect of polypill in the primary prevention of CVD. The main features of these studies are shown in Table 1.

The Indian Polycap Study (TIPS) [55] was a Phase II, double-blind, randomized trial of the Polycap™ once-daily (containing hydrochlorothiazide 12.5 mg, atenolol 50 mg, ramipril 5 mg, simvastatin 20 mg and aspirin 100 mg) compared with eight other groups of aspirin alone, simvastatin alone, hydrochlorothiazide alone, three combinations of the two BP lowering drugs, three BP lowering drugs alone, or three BP lowering drugs plus aspirin in 2053 individuals without CVD, aged 45–80 years, and with one CVD risk factor. This study employed a partial factorial design and randomly assigned participants to nine treatment groups (412 participants to the Polycap group and approximately 200 to each of the other eight treatment strategies and combination CV medications) for 12 weeks. Compared with the appropriate control group (BP-lowering drugs alone and in combination, simvastatin alone and aspirin alone), the Polycap reduced systolic BP (SBP; -7.4 mm Hg; 95% CI: 6.1–8.1), diastolic BP (DBP) (-5.6 mm Hg; 95% CI: 4.7–6.4), LDL (-0.70 mmol/l; 95% CI: 0.62–0.78), heart rate (-7.0 beats per min) and 11-dehydrothromboxane B2 (-283.1 ng/mmol creatinine; 95% CI: 229.1–337.0). Overall, the Polycap was found to be noninferior to its individual components in its effect on BP and heart rate. Reduction in LDL-C and 11-dehydrothromboxane B2 was substantial with polypill, but slightly less as compared with the simvastatin or aspirin alone, respectively. Tolerability of Polycap was found to be similar to that of separate treatments. Although the authors have not clearly mentioned whether participants were on any other concomitant antihypertensive or other medications during the trial that might influence the results, based on the observed short term changes in risk factors, the authors theoretically predicted reductions of CHD by 62% and stroke by 48%. Furthermore, the authors have stated that participants with one risk factor for CVD are enrolled; however, a third of the participants had diabetes in which clustering of CVD risk factors is known to be common. Therefore, it would be important to see whether the proposed polypill retains the benefits of its components when given in purely primary prevention populations. A relatively small sample size and high drop-out rates (16% discontinued study medication) resulting in unavailability of primary outcome data, with short follow-up duration (especially for 206 participants it was reduced to only 8 weeks due to study drugs expiry) were the major shortfalls of the TIPS study.

Malekzadeh *et al.* conducted a double-blind, randomized, placebo-controlled trial of polypill in Iran involving 475 elderly individuals (aged 50–79 years) without CVD and who were not on statins, aspirin or BP-lowering agents [56]. Following an 8-week placebo run-in period, participants were randomized to polypill (aspirin 81 mg, enalapril 2.5 mg, atorvastatin 20 mg and hydrochlorothiazide 12.5 mg) or placebo once daily for a period of 12 months. Polypill reduced SBP (-4.5 mm Hg; $p < 0.001$), DBP (-1.6 mmHg; $p < 0.032$), LDL-C (-0.46 mmol/l; $p < 0.001$), total cholesterol (-0.63 mmol/l; $p < 0.001$), and triglycerides (-0.16 mmol/l; $p = 0.005$) in comparison to placebo. HDL-cholesterol was +0.01 mmol/l higher ($p = 0.575$) and fasting glucose was -0.17 mmol/l lower ($p = 0.008$) in the polypill group compared with the placebo group. Although fewer adverse events were reported, more patients discontinued the polypill than the placebo at 1 month follow-up visit (13 vs 9%). This study showed moderate reduction in risk factors with a predicted 34% reduction in CHD risk and 21% reduction in stroke. At an initial stage of screening for eligibility, participants whose compliance was poor (<70% of pill intake) were excluded, which might result in selection bias and affects the generalizability of the trial results. Although the trial design is that of placebo-controlled trial, the authors have stated that six participants in the control group were started on additional drugs for hypertension (Fisher exact test 2-sided $p = 0.03$) that might dilute the final results, which is analyzed using intention-to-treat (ITT). In addition, statistically significant difference in baseline BP and gender between polypill and placebo groups were observed, which implies that randomization process was not successful and the authors are unable to clarify on this. Higher drop-outs, a narrow age group (elderly age group 50–79 years) of study participants and failure to recruit the target sample size (504) were the major limitations of this study, limiting its generalizability; however the follow-up duration was relatively longer (12 months) than TIPS study (3 months).

The PILL collaborative group conducted a randomized, double-blind, placebo-controlled trial of a polypill (aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg and simvastatin 20 mg) or placebo once daily in 378 individuals without an indication to any component of the polypill, but who had an estimated 5-year CVD risk over 7.5% (calculated using Framingham CV risk equation) or if 5.0 to <7.5% with two or more additional CVD risk factors present [57]. At the end of the 12

week treatment period, the polypill demonstrated 'sizeable' reduction in SBP (-9.9 mmHg; 95% CI: 7.7–12.1) and LDL-C (-0.8 mmol/l; 95% CI: 0.6–0.9) compared with placebo. There was also a statistically significant reduction in DBP (-5.3 mmHg; 95% CI: 3.9–6.7; $p < 0.001$), total cholesterol (-0.8 mmol/l; 95% CI: 0.7–1.0; $p < 0.001$) and triglycerides (-0.2 mmol/l; 95% CI: 0.12–0.3; $p = 0.001$). In the polypill group compared with the placebo group an excess of side effects were reported (58 vs 42%; $p = 0.001$), which were attributed to known side effects of the component medicines of polypill; however these side effects usually did not warrant cessation of trial treatment. Generalizability of the trial results might be limited by the fact that the study was underpowered as the target sample size of 400 participants was not reached. In addition, the authors have reported that due to mislabelling of the sequence of treatment packs, 14 participants in the placebo group received the active treatment. This might have diluted the observed difference in primary outcomes as it was analyzed using ITT. The authors concluded that the polypill achieved 'sizeable' reductions in SBP and LDL cholesterol but also caused side effects in approximately one in six study participants and the projected reduction in CHD and stroke was 60 and 56%, respectively. Furthermore, the authors reported 23% discontinuation rate at 12-week follow up.

Soliman *et al.* conducted a WHO-sponsored, open-label, parallel-group, randomized trial of a polypill (containing aspirin 75 mg, simvastatin 20 mg, lisinopril 10 mg and hydrochlorothiazide 12.5 mg) compared with standard care (defined as usual care administered to patients with similar conditions) in Sri Lanka in 216 participants without established CVD, ≥ 50 years old if female and ≥40 years if male and had an estimated 10-year total CVD-risk score ≥20% based on country-specific WHO CVD risk prediction charts [58]. After a 12-week treatment period there was no significant difference in polypill and standard practices in reducing SBP, total cholesterol, or calculated CVD risk over 10 years. Polypill was well tolerated and the adverse effects were comparable in both the arms. Unlike the other studies, trial treatment discontinuation rate was less in this study demonstrating high rate of patient tolerability and acceptability. Short follow up, standard practice group receiving an unusually high level of care after randomization; issues with lack of standardized study measurements and the open-label design of the study were the short comings of this study.

In a recently published study, Wald *et al.* investigated polypill (amlodipine 2.5 mg, losartan 25 mg, hydrochlorothiazide 12.5 mg and simvastatin 40 mg) compared with placebo in a randomized, double-blind, crossover trial in 86 individuals aged 50 years or more, without history of CVD, living in and around London (UK) [59]. At the end of study (after 12 weeks of placebo and 12 weeks polypill treatment or vice versa) polypill reduced mean SBP (-17.9 mmHg; 95% CI: 15.7–20.1) DBP (-9.8 mmHg; 95% CI: -8.1 to -11.5), and LDL-C (-1.4 mmol/l; 95% CI: -1.2–-1.6). Also, there was significant reduction in total cholesterol (-1.6 mmol/l; 95% CI: -1.8–-1.3), triglycerides (-0.4 mmol/l; 95% CI: -0.6–-0.2 mmol/l) and ApoB (-0.4 g/l; 95% CI: -0.4–-0.3). Polypill was well tolerated (no trial treatment discontinuation due to adverse events) and adherence was good (98% of the participants took more than 85% of their allocated pills), which could be attributed to recruitment of participants who were already on BP-lowering agents and statins. The polypill investigated excluded aspirin, considering the risk of bleeding in individuals without CVD. In conclusion, the authors demonstrated reduction in CHD and stroke risk by 72 and 62% respectively as they predicted. However it was acknowledged that adherence to polypill within the study will not help estimate the adherence in real world settings, also the tolerability to polypill in individuals not on BP-lowering agents and statins would be different to what is observed in individuals who are already on these agents.

In summary, all five studies were pilot/feasibility studies undertaken to assess the short-term safety and efficacy of polypill in primary prevention of CVD. Most established safety, and at least moderate efficacy with the exception of the open-label WHO study. The relatively short follow up precluded the assessment of the long-term drop-out rates and lack of attribution of which component caused which side effects were some of the limitations of these trials. The predicted CV risk reduction was based on the reduction in risk factor levels but these are indirect measures estimating long-term mortality benefits. The findings of these studies were not pooled considering heterogeneity of the study population (Tables 2 & 3), methodological and outcome measure differences, in addition to the variability of polypill composition.

The trial by Wald *et al.* differs from all other primary prevention polypill trials by using a crossover design rather than a parallel group design. The important implications that follow from this are threefold:

- The estimates of efficacy (on BP and cholesterol reduction) in the crossover trial are more accurate (from exploratory perspective);

Table 2. Main baseline characteristics of participants in five polypill trials in primary prevention of cardiovascular disease.

	TIPS [55]	Malekzadeh *et al.* [56]	PILL [57]	WHO study [58]	Wald *et al.* [59]
Participants screened for eligibility	–	1733	859	591	116
Participants randomized	2053	475 (27%)	378 (44%)	216 (37%)	86 (74%)
Participants who completed trial	1727 (84.1%)	348 (73.3%)	338 (89.4%)	203 (94%)	84 (98%)
Female gender	901 (43.9%)	160 (33.0%)	73 (19%)	157 (72.7%)	22 (26%)
Age (years)	54.0 ± 7.9	59.05 ± 6.9	61.4 ± 7.2	59.1 ± 7.2	59 (51–77)
Smoking	276 (13.4%)	101 (21.2%)	153 (40.4%)	24 (11.2%)	8 (9%)
SBP (mmHg)	134.4 ± 12.3	127.5 ± 17.35	134 ± 13.5	165.2 ± 18.2	143 ± 16
DBP (mmHg)	85.0 ± 8.1	79.8 ± 10.05	80.7 ± 9	–	86 ± 10
HR (bpm)	80.1 ± 10.7	–	–	–	–
LDL-C (mmol/l)	3.0 ± 0.8	2.9 ± 0.6	3.65 ± 0.9	–	3.7 ± 0.9
T-C (mmol/l)	4.7 ± 0.9	5.2 ± 1	5.5 ± 1.05	5.9 ± 1.3	5.9 ± 1.0
HDL-C (mmol/l)	1.1 ± 0.3	1.12 ± 0.26	1.25 ± 0.35	–	1.4 ± 0.4
TGs (mmol/l)	1.9 ± 1.2	–	–	–	1.8 ± 1.0
BMI	26.3 ± 4.5	26.2 ± 4.2	–	24.7 ± 10.2	28 ± 4

BMI: Body mass index; DBP: Diastolic blood pressure; HDL-C: HDL-cholesterol; HR: Heart rate; LDL-C: LDL-cholesterol; SBP: Systolic blood pressure; T-C: Total cholesterol; TGs: Triglycerides.

- The cross-over trial results demonstrated almost exactly the predicted changes in BP and cholesterol, whilst the parallel group trials estimates were quite low;
- The predicted effects of the polypill components can be used to estimate the combined effect, which implies that new trials might not be required every time small changes to a FDC/polypill formulation (e.g., a reduction in the dose of BP-lowering drug or statins) are used.

From exploratory trial perspective, the study by Wald *et al.* has more accurately predicted the reductions in BP and cholesterol using polypill than those in the parallel group trials because the results of a parallel group trial need to be analyzed on an ITT basis to avoid selection bias, so patients who did not adhere to treatment (stopped taking the polypill partially or completely) still need to be included, which reduces the estimate of the full pharmacological efficacy. From the trial reports, as many as 23% of patients did not adhere to their prescribed treatment in the parallel group trials. This problem does not arise in a crossover trial because each person is their own control, so anyone not completing the trial can be excluded without introducing selection bias but would seriously impact generalizability as the results would be applicable only to a population that adheres to prescribed therapy. Such groups are difficult to find in routine clinical practice. In contrast, the other four parallel-group primary-prevention trials are pragmatic and adhere closely to real world scenarios where some people are adherent to prescribed treatment and others are not.

Definitive evidence to support the use of the polypill in primary prevention of CVD is awaited from large-scale RCTs with hard clinical end points.

Clinical trials of the polypill in secondary prevention of CVD

While use of a polypill for primary prevention of CVD has been debated extensively over the past decade, its potential use in secondary prevention has been less controversial. A number of trials evaluating the polypill in this context are ongoing (Table 4). As far as the authors are aware, there are seven polypill trials that are currently ongoing and/or proposed for testing the safety, tolerability and effectiveness of polypill among patients at high CVD risk or with established CVD. Of these seven trials, two major polypill trialist collaborations have emerged through public–private partnerships between the large pharmaceutical companies and academic institutions.

One such consortium Single Pill to Avert Cardiovascular Events (SPACE) is a network of international investigators who are conducting or planning a series of polypill trials in secondary prevention of CVDs. Under the SPACE collaboration, currently three parallel, randomized, controlled,

Table 3. Baseline characteristics of study participants in the five primary prevention polypill trials.

Outcome	TIPS [55]	Malekzadeh *et al.* [56]	PILL [57]	WHO study [58]	Wald *et al.* [59]
Participants in the polypill vs control arm	412 vs 1641 (~200 each in eight other groups)	241 vs 234	189 vs 189	105 vs 111	86 crossover design
Drop outs (polypill vs control arm)	64 vs 262 (all combined)	13 vs 9	21 vs 19	6 vs 7	2
Rate of discontinuation of polypill (%)	16	5.4	23	6	2
Major side effects reported	Hypotension, cough, gastritis	Cough	Hypotension, cough, gastritis	Musculoskeletal pain, cough, epigastric pain	Muscle ache
SBP (mmHg)	-7.4	-4.5	-9.9	1.9†	-17.9
DBP (mmHg)	-5.6	-1.6	-5.3	–	-9.8
HR (bpm)	-7	–	–	–	–
LDL-C (mmol/l)	-0.7	-0.46	-0.8	-	-1.4
T-C (mmol/l)	–	-1.6	-0.8	0.4†	-1.6
HDL-C (mmol/l)	–	0.01	0.02	–	0.03
TGs (mmol/l)	–	-0.16	-0.2	–	-0.4
11-dTXB2 (ng/mmol)	-283.1	–	–	–	–
Estimated CVD risk reduction (%)	CHD 62 Stroke 48	CHD 34 Stroke 21	CHD 60 Stroke 56	–	CHD 72 Stroke 64

†Statistically not significant.

11-dTXB2: 11-dehydrothromboxane B2; CHD: coronary heart disease; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; HDL-C: HDL cholesterol; HR: Heart rate; LDL-C: LDL cholesterol; SBP: Systolic blood pressure; T-C: Total Cholesterol; TGs: Triglycerides.

open-label polypill trials are underway, all of which have secured independent funding through peer-reviewed grants such as UMPIRE involving 2000 participants in Europe and India [101,102], IMPACT involving 600 participants (including 300 Maori participants) in New Zealand and Kaniyini–GAP trial [60] recruiting approximately 1000 individuals at high risk of CVD, within aboriginal community-controlled health services and general medical practices in Australia, with an average follow up of 18 months.

The protocol of these three polypill trials is almost identical and the primary outcomes are self-reported adherence to prescribed CVD medications, and change in BP and cholesterol levels from baseline to end of study. Secondary outcomes include acceptability, cost–effectiveness analysis and a formal process evaluation. The polypill used in each of these trials is manufactured by an Indian generic drug manufacturer, Dr Reddy's Laboratories, and there are two versions of polypill being investigated – Red Heart Pill (RHP) 1c containing aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg and atenolol 50 mg (proposed to be suitable for post-MI patients) and RHP 2c containing aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg and hydrochlorothiazide 12.5 mg (considered to be well suited to post-stroke patients). In addition, the IMPACT trial has the provision to use an optional 2-week starter pack – low-dose polypill, available in two versions as follows: RHP 1a (aspirin 75 mg, simvastatin 10 mg, lisinopril 5 mg, atenolol 25 mg) and RHP 2a (aspirin 75 mg, simvastatin 10 mg, lisinopril 5 mg, hydrochlorothiazide 12.5 mg). Collectively, data from these three trials can be pooled to evaluate the impact of polypill on strong surrogate biological outcomes; for instance, changes in BP and cholesterol can be modelled together with the expected effect of aspirin (present in the polypill and taken by some controls) to provide the proportional reduction in CV events.

The other consortium of polypill trialists is FOCUS and constitutes nine institutions across Europe. The FOCUS consortium have planned to conduct a two-phase study, where Phase I is a baseline survey to gather information on proportion of ischemic heart disease patients receiving the CV prevention medications and Phase II will be a randomized controlled trial comparing the CNIC Ferrer polypill containing aspirin 100 mg, ramipril (2.5, 5 or 10 mg), simvastatin 40 mg with conventional treatment with built in prospective economic evaluation [61].

Table 4. Main features of polypill trials in secondary prevention of cardiovascular disease.

	TIPS – K [205]	UMPIRE [209]	IMPACT [26]	Kanyini – GAP [60]	SPACE [73]	CNIC-FERRER (FOCUS) [61]
Funders/ sponsors/ principal investigator	Cadila Pharmaceuticals (India Ltd., Ahemdabad, India)/Salim Yusuf	European Commission (FP7 Grant)/ Imperial College (London, UK)/Simon Thom	Health Research Council of New Zealand/ The National Heart Foundation of New Zealand/C Raina Elley	National Health and Medical Research Council/Anushka Patel	Hospital do Coracao/ Otavio Berwanger	Centro Nacional de Enfermedades Cardiovasculares/ Ferrer Internacional – Spanish pharmaceutical/ Valentin Fuster
Trial registration	CTRI/2010/091/000054	NCT01057537 CTRI/2010/091/000250	ACTRN12606000067572	ACTRN126080005833347	NCT01313702	NCT01321255
Phase of trial	III/IV	III	III	III	III	III
Trial design	Double-blind, randomized, factorial design	Open-label, randomized, controlled, parallel group	Open-label, randomized, controlled, parallel group	Open-label, randomized, controlled, clinical trial	Open-label, randomized, controlled, clinical trial	Open-label, randomized, controlled trial
Countries	India	India, UK, The Netherlands, Ireland	New Zealand	Australia	Brazil	Argentina, Brazil, Italy, Paraguay, Spain
Target sample size	500	2000	600	1000	2000	4000
Main inclusion criteria	M/F ≥ 40 Y, with established CVD and high BP	M/F ≥ 18 Y with established CVD or 5-Y CVD risk of ≥15%	M/F adults with established CVD or 5-Y CVD risk of ≥15%	M/F ≥ 18 Y with established CVD or 5-Y CVD risk of ≥15%	M/F adults with established CVD or 5-Y CVD risk of ≥15%	M/F ≥ 40 Y with history of acute MI (≤ 2Y)
Main exclusion criteria	Contraindication or intolerance to any of the polypill components	Contraindication or intolerance to any of the polypill components	Contraindication or intolerance to any of the polypill components	Contraindication or intolerance to any of the polypill components	Contraindication or intolerance to any of the polypill components	Contraindication or intolerance to any of the polypill components
Intervention (polypill manufacturer)	Polycap: aspirin 100, atenolol 50, ramipril 5, HCZT 12.5, simvastatin 20 mg; potassium citrate – 30 mEq once a day (Cadila Pharmaceuticals Ltd., India)	RHP 1C: aspirin 75, simvastatin 40, lisinopril 10, atenolol 50 mg; RHP 2C: aspirin 75, simvastatin 40, lisinopril 10, HCZT 12.5 mg (DRL)	RHP 1C: aspirin 75 simvastatin 40, lisinopril 10, atenolol 50 mg; RHP 2C: aspirin 75, simvastatin 40, lisinopril 10, HCZT 12.5 mg (DRL)	RHP 1C: aspirin 75, simvastatin 40, lisinopril 10, atenolol 50 mg; RHP 2C: aspirin 75 simvastatin 40, lisinopril 10, HCZT 12.5 mg (DRL)	RHP 1C: aspirin 75, simvastatin 40, lisinopril 10, atenolol 50 mg; RHP 2C: aspirin 75, simvastatin 40, lisinopril 10, HCZT 12.5 mg	Aspirin 100, ramipril 2.5, 5, or 10, simvastatin 40 mg (CNIC Ferrer)

ACEI: ACE inhibitor; BP: Blood presure; CNIC: Centro Nacional de Investigaciones Cardiovasculares; CVD: Cardiovascular disease; DRL: Dr Reddy's laboratories; F: Female; HCTZ: Hydrochlorothiazide; LDL-C: LDL-cholesterol; M: Male; MI: Myocardial infarction; RHP: Red Heart Pill; Y: years.

Table 4. Main features of polypill trials in secondary prevention of cardiovascular disease (cont.).

	TIPS – K [205]	UMPIRE [209]	IMPACT [26]	Kanyini – GAP [60]	SPACE [73]	CNIC-FERRER (FOCUS) [61]
Comparator	One dose of Polycap vs two doses of Polycap, with and without K+ supplement	Usual care	Usual care	Usual care	Usual care	Usual care
Primary outcome	Change in BP and cholesterol from baseline to end of trial (8 weeks)	Adherence to indicated medications change in BP, change in LDL-C, from baseline to end of trial (at least 12 months)	Adherence to indicated medications change in BP, change in LDL-C, from baseline to end of trial (at least 12 months)	Adherence to medications, change in BP, change in LDL-C, from baseline to end of trial (at least 12 months)	Adherence to indicated medications change in BP, change in LDL-C, from baseline to end of trial (at least 12 months)	Percentage of patients prescribed aspirin, ACEIs, beta blockers, and statins, adherence to treatment (at least 12 months)
Follow-up duration	12 weeks with 8 weeks of treatment	Average 18 months	Average 18 months	Average 18 months	Average 18 months	9 months
Trial duration	6 months	36 months; start date: February 2010–January 2013	3 years	2 years; start October 2012; completion July 2014	3 years	18 months
Status	Completed – results awaited	Recruitment completed and currently in follow-up phase	Follow-up phase	Not yet recruiting	Follow-up phase	Recruiting

ACEI: ACE inhibitor; BP: Blood presure; CNIC: Centro Nacional de Investigaciones Cardiovasculares; CVD: Cardiovascular disease; DRL: Dr Reddy's laboratories; F: Female; HCTZ: Hydrochlorothiazide; LDL-C: LDL-cholesterol; M: Male; MI: Myocardial infarction; RHP: Red Heart Pill; Y: years.

In the USA, Cardiopharma, Inc. had filed a new drug application to the US FDA in 2007 for testing a three-drug combination pill – cardiapill containing aspirin, lovastatin and lisinopril [204]. However, no further detail on individual medicine doses and progress toward its clinical testing is publicly available.

Apart from the trials investigating the effectiveness of polypill on adherence in high-risk and established CVD patients, another secondary prevention polypill trial, TIPS-K [205], has attempted to establish whether a double dose of the low-strength Polycap can be safely given and tolerated in patients with established CVD, by demonstrating a superior reduction in mean BP and serum cholesterol at the end of the trial from baseline. TIPS-K is a randomized double-blind, parallel-group 2×2 factorial, multicenter trial that compares the safety and efficacy of two capsules of Polycap (five-drug combination, i.e., aspirin 100 mg, atenolol 50 mg, ramipril 5 mg, hydrochlorothiazide 12.5 mg and simvastatin 20 mg) versus one capsule of Polycap along with or without potassium citrate supplement (open-label daily dose of 30 mEq).

Discussion of key themes: a way forward

This review article has described the rationale behind a FDC or the polypill concept and summarized the published and ongoing FDC/polypill trials both in the primary and secondary prevention settings.

■ Primary Prevention of CVD: evidence from trials are needed to demonstrate polypill benefits in event-based outcomes

The individual level approach in primary prevention that uses a high-risk strategy is not yet proven to be cost-effective with risk prediction being inaccurate. Although lifestyle interventions, health policy, environmental changes and individual behavioural changes are the best explored strategies in primary prevention with perceived low-cost, safety and simplicity; in reality, most of these are not affordable and generally have unsustainable impact. A theoretical complementary approach to prevent the majority of CVD events in both high- and low-income countries could be to administer a FDC/polypill, once daily. However, there are safety concerns related to the administration of FDC/polypill in low-risk individuals. Nonavailability of data on actual rate of side effects due to long term treatment and adherence is another concern in

primary prevention. Thus the criteria for registration of FDC/polypill in primary prevention are more stringent [206,62,63].

The trials of FDC/polypill in primary prevention of CVD that are described in the above section have all tested different versions of FDC/polypill ranging from five to four drugs combination at varied doses.

Of the various components proposed by Wald and Law (six-drug combination pill), lowering of homocysteine by folic acid did not translate into significant benefits in CVD events and hence was excluded from FDC/polypill designed for CVD prevention [37–39]. Additionally due to relatively higher risk of bleeding in individuals without CVD compared with expected benefits, inclusion of aspirin in FDC pill for primary prevention is inconclusive.

Despite primary prevention trials attempting to answer questions related to feasibility of FDC/polypill strategy, several unanswered questions remain (Figure 1) [22]. The recently completed primary prevention FDC/polypill trials have relatively small sample size, heterogeneous study design, polypill composition, varied comparator (placebo vs standard care), analytical methods, outcome indicators, short follow-up period and lack of global representation of patients – all of which limits the generalizability of trial results.

Figure 1. Unanswered questions concerning the polypill strategy.
1°: Primary; 2°: Secondary; CVD: Cardiovascular diseases; FDC: fixed-dose combinations.

Clear and strong evidence on mortality outcomes are not available when four or five drugs are combined in one pill. This is of particular relevance when we are dealing with individuals with low risk, as in primary prevention where the ultimate benefits are the difference between benefits and side effects. The classic examples from literature include antioxidants, hormone-replacement therapy and to some extent even intensive salt reduction, all of which have huge benefits in reducing intermediate outcomes but no benefit in reducing CV mortality [64–67].

Decision-driving evidence is awaited for FDC/polypill use in primary prevention among different populations or regions. Large outcome trials of FDC/polypill involving wide representation of primary populations across the world are needed to provide answers to major questions, alluded to in Figure 1, and might also facilitate the licensing of a FDC/polypill for general preventive use.

■ Secondary prevention: evidences from trials are available on combination therapy of multiple drugs used in increments with event-based outcomes

The WHO PREMISE study (2003), a cross-sectional survey of current practice patterns involving 10,000 CVD patients, concluded that there were considerable missed opportunities for appropriate medication prescription, processes of care and lifestyle advise for smoking cessation, healthy diet and physical activity to prevent recurrences in established CVD patients [68]. The study also concluded that only about a fifth of CVD patients received statins and BP-lowering medications [68]. Non-prescription of proven therapies and non-adherence to physician prescriptions are major barriers in implementation of secondary prevention because medication discontinuation is associated with higher rates of recurrent events and mortality in patients with existing CVD [69,70].

Based on available clinical data on individual components, polypill can be used in secondary prevention, high-risk primary prevention and an anticipated 50–70% risk reduction is expected on prolonged therapy. However there is insufficient evidence to support the use of polypill in those without CVD and in individuals

who are not at high risk. The results of currently ongoing FDC/polypill trials in secondary prevention will provide new evidence as to whether or not a FDC/polypill-based treatment strategy improves adherence to prescribed CV medications amongst individuals in whom these treatments are indicated.

In order to reach clinical conclusions, for an estimated 20% relative-risk reduction of CVD events, we would require over 13,000 patients to be randomized. On the other hand, to prove FDC/polypill treatment as noninferior to usual care, with hazard rate of 1.5 we would require over 11,000 patients to be randomized. A range of calculations for different event rates in the control group over 1.5 years, against different levels of risk reduction is presented in Table 5 and for different hazard ratio is shown in Table 6 for noninferiority testing.

Table 5. Numbers required (ideal sample sizes) to reach clinical conclusions using polypill-based treatment strategy in high-risk population.

Cumulative event rate in control group at 1.5 year (%)	15% RR reduction (n)	20% RR reduction (n)	25% RR reduction (n)
5	25,000	13,500	8500
7.5	16,000	9000	5500
10	12,000	6500	4000

RR: Relative risk.

Table 6. Numbers required for noninferiority testing of polypill compared with usual care in high-risk population.

Cumulative event rate in control group (%)	Hazard rate 0 = 1.25 (n)	Hazard rate 0 = 1.5 (n)
5	37,500	11,500
7.5	25,000	7500
10	18,500	6000

Regions of the world where FDC/polypill trials have been studied & its impact

Among the primary prevention studies, with the exception of Wald and Law's trial, which focused only on one region – northern Europe – all other studies represented south-central Asia. Whilst the study conducted by the PILL collaborators also covered regions such as Australia, South America, northern Europe and North America, fewer participants were recruited in the North and South American regions. Amongst the six secondary prevention studies, only two are currently on-going in south-central Asia, whilst two are being carried out in the Australian and South American regions, and one each is running in north, west and southern Europe (Figure 2).

Given that CVD in LMICs is the biggest cause of death and loss of healthy life years, the high burden of CVD amongst economically productive adults results in huge economic losses. Since the constituents of the CV polypills used are all generic/off-patent, there is

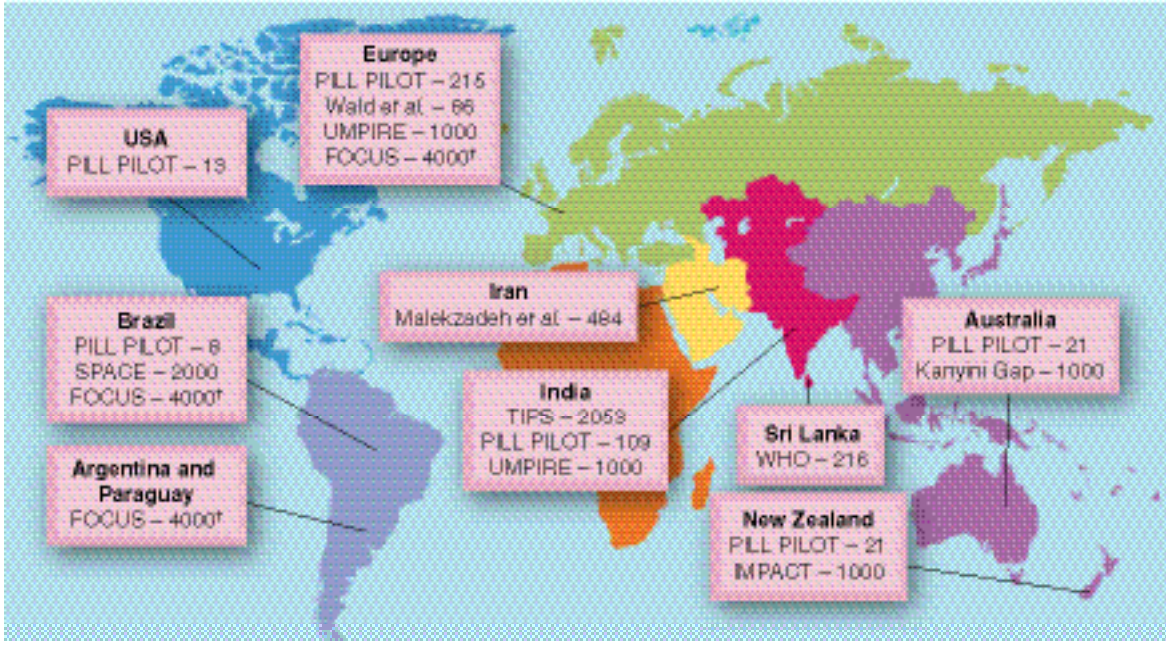

Figure 2. World map showing the regions of the world where polypill trials are ongoing or completed.
†Total sample size.

scope to keep the cost down through competition. This has particular relevance to the LMICs as most health care in these countries is paid for out-of-pocket and cost to the patient is likely to be the most important factor impeding preventive care. Additionally, a substantial part of the population who are currently deprived of effective secondary preventive treatments would benefit from a low-cost polypill treatment. Despite the WHO's 1999 report, that indicated CVD is the second most common cause of death in African countries accounting for 11% of total deaths and a major cause of chronic illness projected to double by 2020 [207,208]; surprisingly, none of the polypill studies were conducted in African regions. A possible reason for this could be the regions to which the different consortium of FDC/polypill trialists (FOCUS and SPACE collaborators) belong. Other reasons may include feasibility, non-availability of funds, lack of local government initiatives, pharmaceutical companies' profit margin and cost–effectiveness of doing trials in African region and so on.

In summary, despite the theoretical benefits of the FDC/polypill treatment strategy, the FDC/polypill concept has been challenged by many clinicians and public health researchers. Major concerns include the compatibility of the ingredients, pharmacokinetics, safety, tolerability, drug interactions, difficulty in dose titration in case of patients who will not reach the target goals [71], cost–effectiveness, generalizability to different patient groups, long-term adherence as well as the 'medicalization' of population-based prevention. Many researchers argue that a FDC/polypill-based treatment strategy may interfere with lifestyle modification approaches [72]. By contrast, others suggest that due to FDC/polypill use, physicians may need to spend less time on tests and titration and therefore could devote more time on lifestyle change advice. Furthermore, there is lack of evidence on whether patients and physicians will adopt a FDC/polypill based CVD prevention strategy widely and whether a polypill could improve medication adherence.

Evidence on cost–effectiveness of FDC/polypill strategy is currently limited to modelling estimates, since large FDC/polypill trials with built-in economic evaluations are yet to be completed. If FDC/polypill treatment is proven effective, costing studies will need to answer the overall financial impact of switching patients at high risk of CVD from usual care to a FDC/polypill, as well as qualitative research studies to explore the opportunities and challenges associated with delivering the FDC/polypill at scale in different healthcare settings. With the increasing use of generics, we believe the cost of standard-care treatment for CVD should be low. However, due to huge variations in existing usual care for CVD the actual nationwide comparative figures are not available. For example, it is estimated that for acute coronary syndrome patients in India, the annual cost of treatment (aspirin, clopidogrel, beta blockers, ACE inhibitor and statins) might range from $122 to 362 [Harikrishnan S, India, Unpublished Data]. It is suggested that annual cost of a CV FDC/polypill per individual could be as low as $19 in India and $64 and $186 in other developing and developed economies, respectively, indicating that a polypill/FDC may be reasonably cost-effective in secondary prevention. However it is crucial to note that the ongoing trials have surrogate markers (SBP and LDL-C) as primary end points and not purely clinical end point, which are determinant of cost–effectiveness analyses. If FDC/polypill strategy is proven to be cost-effective based on large outcome trials, it would have the potential to address the issues of affordability and equity.

In light of new evidence that will accumulate from currently on-going trials and results of FDC/polypill trial process evaluation studies, we may be able to overcome some of the perceived barriers of delivering FDC/polypill based treatment strategy such as the autonomy issues (prescription and dose titration) and change from conventional thinking among medical professionals, positioning of lifestyle interventions and complementing it with FDC/polypill, and finally economic and policy issues by engaging patients, governments and pharmaceutical and insurance companies. Of most significance is the role of government agencies in regulating and authorizing the use of FDC/polypills by subsidizing the drug manufacturing costs. In return, the pharmaceutical companies can offer discounts on bulk purchases by governments, recognizing that they are the primary providers of healthcare to the most disadvantaged segments of the population. In parallel to conventionally promoting the polypills to doctors, we recommend the distribution of medication through an expanded network (perhaps through trained community health workers) that reaches the smaller towns and rural areas. However, to enable such wide availability, it is necessary to obtain registration from medicine regulatory authorities and data from on-going trials is crucial for regulatory marketing authorization of FDC/polypill.

Conclusion & future perspective

In less than a decade since the FDC/polypill concept was proposed by Wald and Law, multiple clinical trials have been conducted and the feasibility, tolerability and short-term effectiveness benefits of

Executive summary

- The fixed dose combinations/polypill strategy in cardiovascular disease (CVD) prevention has been debated for a decade now and it seems to have potential to reduce the CVD risk by >50%.
- Existing gaps in adherence to CVD-management guidelines and prescribed treatments, as well as under utilization of essential CVD drugs, may be attributed to a number of factors including complexity of regimen and cost of treatments being major barriers, all of which could be addressed by a fized-dose combination (FDC)/polypill strategy.
- Five pilot/feasibility studies have demonstrated the short-term safety and efficacy of FDC/polypill in primary prevention of CVD; however, the evidence is not convincingly sufficient to endorse the strategy for practice before this is established in large-scale randomized trials with hard clinical end points.
- FDC/polypill is considered as a potential novel strategy, combining both clinical and public health approaches with a pivotal role in the secondary prevention of CVD; however, results from ongoing trials offer much hope for evidence on medications adherence and cost–effectiveness.
- FDC/polypill may complement other lifestyle-modification approaches including reduction in tobacco use, healthy diet and increased physical activity as part of the comprehensive global CVD prevention strategy.

FDC/polypill have been demonstrated. Furthermore, ongoing FDC/polypill trials will establish the impact of FDC/polypill on medication adherence, acceptability, clinical outcomes and economic issues. In order to achieve substantial reduction of CVD burden, immediate use of FDC/polypill in secondary prevention is indicated; however, the evidence in primary prevention need to be adjudicated (though primary prevention FDC/polypill trials have at least predicted 50% CVD-risk reduction).

FDC/polypill might not itself be considered a panacea to tackle the CVD epidemic worldwide. Instead, based on the accumulated evidence from FDC/polypill trials so far, we advocate for a four-pronged approach comprising of reduction in tobacco use, healthy diet, increased physical activity and cost-effective multidrug/combination CV-preventive drugs (perhaps polypill), in order to have significant reduction in CVD risk burden globally.

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