The Polypill: An Effective Approach to Increasing Adherence and Reducing Cardiovascular Event Risk

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ABSTRACT

Background: Despite a wide range of medications available for the prevention of cardiovascular events such as stroke, myocardial infarction and mortality in both a primary and secondary setting, patient adherence to complex therapy regimes involving different drug classes remains low worldwide. Combining anti-platelet, antihypertensive, lipid-lowering and potentially further drugs into one "polypill" has the potential to increase adherence, thereby reducing risk factors to a greater extent and for a longer duration. The WHO has recently highlighted increased adherence as a key development need for reducing cardiovascular disease.

Areas covered: Recent clinical trial data regarding adherence, reductions in cardiovascular risk and outcomes, safety and tolerability, and cost-effectiveness of the polypill approach are summarised and reviewed. In addition, ongoing trials and the questions they intend to answer are considered. References were retrieved from a PubMed literature search (date range 1990-2016) using the terms "polypill", "cardiovascular events" and "adherence", and selected based on relevancy. The website www.clinicaltrials.gov was also consulted for identification of ongoing trials.

Conclusions: To date, the polypill approach has been conclusively shown to increase adherence relative to usual care in all patients, with those in a primary care setting or with poor baseline adherence potentially standing to benefit most. Concomitant risk factor reductions have also been suggested. However, whether this translates into a reduction in cardiovascular events and generates good cost-effectiveness in a given healthcare environment is currently under further investigation.

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Key words: Adherence, polypill, systolic blood pressure, LDL-cholesterol, cardiovascular events/outcomes

INTRODUCTION

Cardiovascular disease (CVD) is a principal global concern responsible for approximately 17.3 million deaths annually; a figure projected to reach >23.6 million by 2030 [1]. For patients at risk of cardiovascular events such as myocardial infarction (MI) and stroke, prevention is commonly achieved via long-term pharmacological treatment with anti-platelet drugs, β-blockers, angiotensin converting enzyme inhibitors (ACEIs)/ angiotensin-II receptor blockers (ARBs) and statins, and multiple therapeutic agents are often prescribed concomitantly in order to attain full prophylactic effect. Combination therapy using a statin, aspirin and an antihypertensive agent has been associated with reductions in MI, stroke, and mortality risk compared to monotherapy [2], and an 80% reduction in overall cardiovascular event risk when aspirin, β-blockers, lipid-lowering drugs and ACE inhibitors are used simultaneously has been estimated [3].

However, problems with adherence (defined as "the extent to which the patient follows medical instructions" [4]) frequently accompany polypharmacy; leading to reduced efficacy [5]. Worldwide, an estimated 50% of CVD patients employing therapeutic agents as a primary prevention measure and 43% as a secondary prevention measure fail to adhere to treatment programs in the first 2 years [6]. Furthermore, when stratified by drug class, a recent meta-analysis of 34 studies showed that 46% of patients on statins, 41% on antihypertensive agents, and 30% on aspirin fail to adhere to their medication [7]. Though there are a range of sociodemographic, psychological, economic and clinical factors that have been associated with nonadherence, complexity of treatment regimes and pill burden have been widely recognised as principal contributors [5, 7-10].

It has recently been suggested that by improving adherence by 10%, the incidence of cardiovascular events (both fatal and non-fatal) can be reduced by 6.7% [11]. Indeed, expert panels such as the World Health Organisation (WHO) advocate addressing the factors contributing to nonadherence as a fundamental priority over development of specific evidence-based drugs for improving cardiovascular health outcomes [4]. The combination of individual agents into one "polypill" has been shown to reduce pill burden [12], and therefore offers a potential method for improving adherence.

A review of available literature is in order given that many published studies focus on one particular polypill, setting or population, while the polypill has many variants and is applicable worldwide. Latest reviews do not include some of the most recently published evidence, such as the SPACE meta-analysis which is the first prospective study with suitable statistical power to answer several important questions about the efficacy of the polypill for risk reduction [13]. Here, we review the existing and ongoing studies into the polypill with the aim of providing a thorough overview of progress to date.

THE POLYPILL

The polypill approach to cardiovascular event prophylaxis was first conceptualised by Wald and Law in 2000, in which five commonly used preventative medications were combined into a single pill [14]. Nowadays, multiple fixed-dose combination polypills are available with differing active components, applications (primary vs. secondary prevention), and doses. An overview of the most well-documented polypills can be seen in **Table 1**. In general, each polypill is composed of a minimum of a statin, an anti-platelet drug (commonly aspirin), and an antihypertensive agent (ACEI/ ARB/ thiazide/ β-blocker/ calcium-channel blocker) each selected based on clinical trial efficacy and pharmacological interaction data [15, 16]. A UK, open, prospective cohort study assessing the relative reductions in cardiovascular risk for a range of medicinal permutations found that a combination of statins, aspirin, and β-blockers were the most effective (reductions of 83%), followed by a combination of statins, aspirin, and ACEIs (reduction of 71%) [16]. It therefore follows that these are the most common combinations for polypills, though aspirin is often omitted for primary prevention due to unjustifiably increased bleeding risk [17].

In pharmaceutical terms, ensuring that the final polypill has a bioequivalence equal to its monocomponents is not straightforward, and formulation becomes linearly more difficult for every agent added [18]. This is for a number of reasons, including incompatibility of chemical and physical stability properties (solubility, sensitivity to heat and moisture), and complications in purification and bioanalytical processes owing to large differences between dose magnitudes [18]. The probability of drug interactions is also increased by the number of components included in the polypill, further limiting feasibility [10]. In some instances, specific sequencing of drugs within the polypill is necessary, as can be seen in the patterning of Trinomia® , to avoid the physicochemical incompatibilities between the active ingredients while preserving their biopharmaceutical and pharmacokinetic properties [18, 19]. Furthermore, selection of components that do not exclude large subsets of the population (such as asthmatic patients in whom β-blockers are contraindicated) further complicates the polypill development process. These pharmacological limitations mean that although multiple polypills are available, it is unrealistic to expect an unlimited choice of combinations. That said, as most of these therapies have been used in separate pill combinations for many years, the risk/benefit profiles are well established, meaning that effects and safety can be predicted with reasonable certainty and development costs are unlikely to be wasted.

A range of studies assessing the safety and tolerability, efficacy, potential for increased adherence and

cost-effectiveness of the polypill approach in primary and secondary prevention have been carried out, and several more are currently ongoing. An overview of important completed studies can be found in **Table 2**, the results of which are summarised below.

ADHERENCE

To date, studies have reported a range of values for good adherence (generally defined as taking practitioner-prescribed medication >80% of the time) to indicated CVD medication in polypill form, measured using various methodologies over differing durations.

Overall Adherence

Several placebo-controlled studies have assessed adherence rates in patients with CVD risk factors only. Such primary prevention patients are generally considered less likely to accept and adhere to multiple pill regimes given the lack of visible symptoms. In a crossover study by Wald et al. comparing the polypill to placebo over 12 week periods in patients with only advanced age as a risk factor, 98% of patients were found to take >85% of their allocated medication while on the polypill (quantified via the pill count method), which was equivalent while on the placebo [17]. Similarly, a double-blind placebo-controlled trial of the Red Heart Pill ™ 2 (**Table 1**) in patients with an estimated 5-year cardiovascular disease risk over 7.5% (PILL), found comparable proportions of patients displaying good adherence in polypill and placebo groups (82% vs 86%) [20]. This suggests that adherence is likely to be related to pill count rather than the pharmacological effects of the polypill, and indicates good acceptance in patients with no obvious CVD symptoms.

When taken in the context of usual care, a recent cross-sectional study including 695 post-MI patients from 4 countries (FOCUS), found that at 9 months post-MI, 50.8% of patients in the intention-to-treat polypill group (Trinomia®- **Table 1**) had ≥80% adherence to treatment compared to only 41.0% in the usual care group based on combined Morisky-Green medication adherence questionnaire (MAQ) and pill count data [8]. Furthermore, levels of adherence increased by an average of 6.7% from baseline to final follow-up in the polypill group [8]. Similarly, the TEMPUS study observed modestly higher adherence levels for morning or evening administration of the polypill compared to standard combination therapy (5.2% and 5.3% for morning and evening administration, respectively) as measured using a microelectronic monitoring device over 6-8 weeks [21]. Relative to other published results, the effect of the polypill on adherence in these two trials appears modest, though both were

performed exclusively in a secondary prevention setting (compared to the primary/ mixed settings of other studies) and measurement approaches differed. As a possible explanation, the FOCUS authors stress the comparatively short trial duration and observed divergence of good adherence frequency between control and polypill groups over time [8].

In longer-term studies such as UMPIRE, Kanyini-GAP and IMPACT (three open-label, randomised trials with the Red Heart Pill™ version 1 or 2 (**Table 1**) over a minimum of 12 months in patients with existing [former two trials] and/or at high risk of CVD [all three trials]), the observed difference in adherence between polypill and usual care groups has been significantly greater. At completion of UMPIRE, IMPACT and Kanyini-GAP, 86.3%, 81% and 70.1% of polypill patients reported good adherence to combined treatment compared to only 64.7%, 46% and 46.9% of usual care patients, respectively [22-24]. Furthermore, a high-power meta-analysis of these three trials including individual data for 3140 participants (SPACE), found that on average 80% of patients were adherent to combination therapy at 12 months post polypill initiation compared to only 50% in the usual care arm (see **Figure 1**) [13].

Discrepancies over the magnitude of the polypill effect are likely due to differences in trial design. In the IMPACT trial, adherence was determined by patients reporting "current use" of an antiplatelet, statin, and a minimum of two blood pressure lowering drugs by naming them at each follow-up visit [25], while the UMPIRE, Kanyini-Gap and SPACE trials required self-reported taking of the aforementioned medication on at least 4 days out of the 7 days preceding the follow-up visit [13, 22, 23]. In both cases, the self-reported nature of adherence quantification is subject to patient "need to please" bias, and this coupled with differences in healthcare settings and patient demographics may also have contributed to the variability in adherence magnitudes. However, the recurring finding that the polypill significantly enhances adherence in all currently published studies suggests the broadly generalisable superiority of the polypill over usual care for this outcome.

Adherence by subgroup

When FOCUS data were adjusted for the covariates depression, social support, insurance coverage, and treatment complexity (which had all previously been associated with adherence in FOCUS phase I) adherence remained significantly higher in polypill patients compared to usual treatment patients, suggesting that the polypill has the capacity to independently increase adherence irrespective of patient circumstances [8]. This trend was also observed in the UMPIRE study, which showed that when follow-up data was analysed by baseline subgroups (primary or secondary prevention, adherence at baseline, sex, diabetes, smoking, continent, and polypill version), greater adherence was seen on the polypill in all cases [23]. However, a larger effect was observed for patients who were non-adherent at

baseline (risk ratio [RR] 3.35 [2.74 - 4.09; p<0.001]), a finding supported by the IMPACT study (RR 5.09 [3.40 - 7.63; p<0.001]) [24], and subsequently reflected in the SPACE meta-analysis (RR 4.46 [3.71-5.36; p<0.0001]) [13]. Importantly, the UMPIRE trial also identified patients at high risk of CVD (and therefore using the polypill as a primary preventative measure) as a key subset of patients in which the polypill had a larger effect on adherence (RR 1.93 [1.51 – 2.47; p<0.001]) [23], a population which was also highlighted by the Kanyini-GAP study (RR 2.17 [1.62 - 2.90; p<0.001]) [22], and subsequently in the SPACE analysis (RR 2.12 [1.77 - 2.54; p<0.0001) [13]. This strengthens the case for polypill use in primary preventative care.

PATIENT WELLBEING

In terms of Quality of Life (QoL), the UMPIRE study reported significantly higher scores on the visual analogue scale (EQ-5D) for the polypill group compared to the standard treatment group, indicating greater levels of patient-perceived health [23]. No differences in QoL were observed during the Kanyini-GAP study using the same questionnaire [22], however study numbers were much smaller and it is possible that effects could not be seen due to low statistical power. Though the IMPACT trial also failed to observe significant differences between treatment groups in terms of QoL, it did document the majority of polypill patients as finding their medication regime “very easy” to take (53% of polypill patients compared to 42% of usual therapy patients); suggesting greater levels of acceptability [24]. This idea is supported by the preference for the polypill over usual care in 92% of patients in the TEMPUS study (a randomised, open blinded end-point, three-period cross-over trial using the polypill Red Heart Pill ™ 2) [21]. Furthermore, patient behavior in terms of changes in body mass index (BMI) / waist circumference / smoking and physical activity levels between baseline and 12 month follow-up did not seem to be affected by use of the polypill in the SPACE analysis [13], and elevated levels of moderate activity were reported by the UMPIRE trial [23]. Overall, this suggests that the polypill does not reduce, and may improve patient wellbeing.

RISK FACTOR CONTROL

As with standard medication for the reduction of CVD risk factors, polypill efficacy has typically been measured in terms of systolic blood pressure (SBP) and LDL-cholesterol (LDL-C) reductions, with conflicting findings.

Risk factor control in placebo-control trials

In the PILL study, SBP and LDL-C reductions were 9.9 mmHg and 0.8 mmol/L relative to placebo at 12-week follow-up, respectively [20]. Though much lower than the risk factor reductions predicted by Wald and Law owing to different polypill components [26], a 48% reduction in risk of cardiovascular events was nonetheless calculated, with greater reductions in patients who had a baseline LDL-C of >3.6 mmol/l or SBP of >135 mmHg [27]. In a later crossover study by Wald et al. comparing the polypill to placebo over 12 weeks in patients with only advanced age as a risk factor, the polypill achieved an almost identical reduction in systolic blood pressure (SBP; 17.9 mmHg [12%]) and LDL-cholesterol (LDL-C; 1.4 mmol/L [39%]) to that predicted by meta-analyses of component parts (18.4 mmHg and 1.4 mmol/L, respectively) [17]. This supports the idea that the polypill approach is equally as efficacious in the reduction of CVD risk factors as its respective component parts.

Risk factor control compared to usual care

In all studies that compare polypill therapy to usual care identified by the literature search, the polypill has been shown to provide at least non-inferior SBP and LDL-C control [8, 12, 21-24, 28]. However, the degree of efficacy remains controversial.

In the FOCUS, IMPACT, TEMPUS and Kanyini-GAP studies, no significant difference in SBP and LDL-C change from baseline were observed between polypill and standard therapy groups at study completion, despite reduced pill counts and improvements in adherence [8, 12, 21, 24]. However, in most of these studies a trend towards polypill superiority was evident, and low patient numbers leading to insufficient statistical power may have been responsible for the apparent lack of significant effect.

Accordingly, the larger-scale UMPIRE trial (2004 patients) found that at study completion, the polypill regime was more effective than usual care in terms of lowering both SBP and LDL-C (treatment effects of -2.6 mmHg and -4.2 mg/dL, respectively); a trend which was observed throughout the study [23]. Furthermore, when analysed by baseline subgroups (established or risk of CVD, adherence at baseline, sex, diabetes, smoking, continent, and polypill version), the polypill resulted in superior SBP and LDL-C reductions in almost all cases, with most pronounced effects on SBP in patients who were nonadherent at baseline (mean difference -4.9 [-7.3 to -2.6; p=0.01]) and male (mean difference -3.3 [-4.9 to -1.7; p=0.03]), and on LDL-C in patients from India (mean difference -10.8 [-14.1 to -7.4; p<0.001]) [23]. These findings were reflected in the large, highly-powered SPACE meta-analysis, which included several of the aforementioned studies in which statistical significance had not previously been seen. In SPACE, both mean SBP and LDL-C levels were significantly lower (-2.5 mmHg and -0.09

mmol/L, respectively) at 12 months for polypill patients compared to baseline (see **Figures 2 and 3** for overview) and adherence was a significant effect modifier for SBP (p=0.02), while age, country and established CVD were significant effect modifiers for LDL-C (p=0.005, <0.001 and =0.017, respectively) [13]. This reconfirms the idea that the lack of significant difference in risk factor reduction between polypill and usual care arms reported by smaller trials is due to insufficient statistical power impeding effect detection.

Effect of timing on risk factor control

In TEMPUS, reductions in fasting LDL-C and overall cholesterol levels in patients administering the polypill in the evening were found to be comparable to combination therapy [21]. However, both of these factors were increased by 0.2 mmol/L when the polypill was administered in the morning. This indicates the benefit of evening polypill administration over morning administration, and is consistent with the idea that simvastatin is more efficacious when taken in the evening [17, 29] Though modest, a reduction of 0.2 mmol/L is reported to correspond to a 10% lower risk of cardiovascular event on a population level [21], suggesting that advising patients to take their medication in the evening could have a considerable impact on patient health. No significant difference in SBP was observed [21]. In contrast among patients receiving atorvastatin 40mg, changes in levels of total cholesterol, LDL-C, triglycerides and HDL-C were similar, regardless of the time of day the drug was administered [30].

Cardiovascular outcomes and mortality

FOCUS found that the frequency of all adverse events (including mortality, reinfarction, and hospitalisation due to cardiovascular reasons) was low and similar between the polypill group (35%) and usual therapy control group (32%) [8]. The IMPACT, Kanyini-GAP and UMPIRE trials also reported similar proportions of patients experiencing cardiovascular outcomes between study groups [22-24] which was, unsurprisingly, reflected in the SPACE analysis [13]. In terms of mortality, the IMPACT and UMPIRE studies also reported similar overall death rates, though in UMPIRE a larger proportion of deaths were vascular-related in the polypill group (82.4%) compared to the usual care group (53.3%) [23, 24]. This finding was not reflected in the SPACE meta-analysis, which saw no significant difference in the frequency of death associated with CVD between groups [13]. Thus, as yet, no clear link between the polypill and improvements in cardiovascular outcome frequencies relative to usual care has been established.

ONGOING OUTCOME TRIALS

The fact that improved adherence and risk factor reduction have not yet been shown to translate into a reduction in cardiovascular outcomes is a concern. However, this is likely due to the relatively short duration of available pilot studies and meta-analyses, given the previously identified 1-2 year lag-phase before the maximum SBP and LDL-C benefits of CVD medication are typically observed [31, 32]. Similarly, low patient numbers in previous trials have lead to a low incidence of cardiovascular events, meaning that it is probable that studies have not been high-powered enough to detect effects. A number of studies in larger patient populations over a considerably extended time-period are currently ongoing to address these limitations and assess the long-term efficacy of the polypill, a summary of which can be seen in **Table 3**.

The TIPS-3 study is a 2x2x2, factorial design, control trial in patients at moderate-high risk of cardiovascular event which will compare the polypill (Polycap®- **Table 1**) to placebo for the prevention of cardiovascular death, stroke and MI [33]. Follow-up is planned over a 5 year period in 5000 patients aged over 55 (men) and 60 (women) from 10 different countries; resulting in a high-powered study from which to obtain conclusive results regarding polypill efficacy. In addition, the potential benefits of combinations of the polypill, vitamin D and aspirin for reducing fracture and cancer risk will also be assessed. Completion is expected in March 2020, and should establish the long-term benefits of the polypill for reducing cardiovascular outcomes with minimal pill burden in a primary prevention setting. An even larger study in primary prevention is the HOPE-3 trial [34]. This is a randomised, placebo-controlled trial in 21 countries evaluating rosuvastatin plus a candesartan/ hydrochlorothiazide pill used singularly or in combination in 12,705 “normal” individuals aged >60 (women) or >55 (men) at medium risk of CVD. The study will last an average of 5.7 years, during which rate of cardiovascular outcomes will be evaluated against placebo. Though in reality two pills will be employed in this study, it will be helpful for demonstrating that reductions in SBP and LDL-C seen in previous trials endure long-term, and translate into increased cardiovascular protection. Findings will be extended in a subsequent phase 4, large-cohort (9500 participants), open-label, parallel cluster, randomised controlled trial (HOPE-4) to assess the benefits of structured education and support networks in addition to the polypill compared to usual care over 6 years [35]. This study will assess the potential for a combination of factors to reduce Framingham risk scores and improve cardiovascular outcomes, and the polypill is expected to contribute substantially to favorable effects.

In terms of secondary prevention, two important trials are ongoing. PROPS is a multi-center, open-label, randomised controlled trial evaluating the blood pressure-lowering efficacy of the polypill

Trinomia® compared to usual care in 1222 patients aged >55 with prior stroke [36]. This is a phase II trial and therefore only planned to last 24 weeks with moderate patient numbers, however further evidence supporting the non-inferiority of the polypill is expected, with results anticipated in 2018. A second, longer-term study with Trinomia® entitled SECURE will assess the potential of the polypill to prevent major cardiovascular events in 3206 elderly patients (>65 years) with recent MI, stroke or coronary revascularization. Follow-up will take place over a minimum of 2 years (maximum 4 years), with completion expected in October 2019 [37]. Results from this study will help to clarify firstly whether increased adherence to medication using the polypill in a secondary prevention setting endures longer-term, and secondly whether this translates into significantly lower frequencies of cardiovascular outcomes when the previously mentioned 1-2 year lag phase is surmounted.

A further study is currently assessing the polypill for both primary and secondary prevention in a low-income country. The PolyIran trial involving approximately 7000 Iranian adults aged >50 aims to compare a polypill containing aspirin 81mg, enalapril 5mg (or valsartan 40mg), atorvastatin 20mg and hydrochlorothiazide 12.5mg to minimal care (education and blood pressure monitoring) or usual care over a period of 5 years [38]. The primary outcome is the amount of time elapsed before first cardiovascular event, with secondary outcomes addressing adherence, risk factor reduction and adverse events. Completion of data collection is expected in April 2018. Though the results of this study will be interesting, use of an Iranian population only may limit the extrapolation of findings on a wider scale.

SAFETY AND TOLERABILITY

Side effects

The PILL study found that the side effects associated with the polypill (predominantly dizziness / hypotension, gastric irritation and cough) were generally identified as those usually associated with its components, and led to 23% of patients discontinuing polypill therapy over 12 weeks [20]. The same side effects were also reported as principal reasons for polypill discontinuation in IMPACT [24], and 28.9% of patients in Kanyini-GAP who discontinued polypill treatment did so primarily due to cough (15.1%) or dizziness / hypotension (5.8%) [22]. Concurrently, SPACE also reported that 35% of treatment discontinuations in the polypill group were due to side effects, the most common of which was cough [13].

In terms of kidney function, a common concern with chronic use of CVD drugs, UMPIRE reported significantly greater elevations in creatinine between baseline and final follow-up for polypill patients (+0.06 mg/dL) compared to usual care patients (+0.03 mg/dL), suggesting greater levels of renal damage [23]. This was accompanied by significantly greater elevations in uric acid (+0.3 mg/dL versus +0.1 mg/dL for polypill and usual care patients, respectively). Concurrently, deterioration in kidney function was given as a principal reason for polypill treatment discontinuation in the IMPACT study [24], though according to the Kanyini-GAP study there was no significant difference in the incidence of renal events between polypill and usual care patients [22]. The SPACE meta-analysis also found no difference in creatinine levels between polypill and usual care groups at 12 months [13].

These data suggest that common side effects associated with the polypill are the same as those associated with individual component parts.

Serious adverse events

Excluding hard outcomes, the proportion of adverse events classed as serious in the FOCUS trial was low and comparable between polypill and usual care groups (6.6% vs. 6%, respectively) [8]; which was also the case, if at a higher frequency, in the Kanyini-GAP, and UMPIRE trials (46.3% versus 40.7, and 11.8% versus 10.2%, respectively) [22, 23]. Disparity between amplitudes is likely due to differences in what is considered "serious", study populations and trial durations; though nonetheless the proportion of patients discontinuing treatment due to adverse events in the FOCUS trial (4% and 3.7% for polypill and usual care groups, respectively) [8] was similar to that observed in the UMPIRE trial (2.6% of polypill patients) [23]. Essentially, these studies suggest that the polypill neither reduces nor enhances the prevalence of serious adverse events associated with usual CVD treatment.

COST-EFFECTIVENESS

An important factor contributing to the success of novel therapies is cost-effectiveness. This is largely dependent on healthcare system willingness to pay, with thresholds differing significantly between countries. However, an original objective of the polypill was to produce a therapy that could be made available even in low-income countries with low cost-effectiveness thresholds [39]. Since then, several analyses estimating polypill cost-effectiveness in different populations and settings have been published.

In a primary prevention setting, polypill cost-analyses have yielded encouraging results. In Latin America, the polypill was estimated to reduce CVD risk by 15% in women and 21% in men at high risk of CVD, with a high degree of cost-effectiveness applicable even to extremely low-income countries such as Peru; particularly when distributed to males aged over 55 years and women at >15% risk of CVD (incremental cost-effectiveness ratio [ICER] of $268 per quality adjusted life year [QALY] gained) [40]. A second study in primary CVD prevention found that compared to statins, low-dose diuretics and ACE-Is, the polypill was the most cost-effective for treatment of Australia´s indigenous population based on medication costs, practitioner visits, and blood tests over time. This led to an approximate annual saving of up to $21,000 per disability-adjusted life-year where cost of the polypill was $500 per subject year [41]. A further study in the Thai population suggested a high degree of cost-effectiveness for the polypill which proved dominant in all patients with a 10-year CVD risk >5% [42]. Therefore, as a primary care measure the polypill appears highly cost-effective in a wide range of healthcare systems.

In terms of secondary prevention, a study in a hypothetical, >65 year old, post-cardiovascular event, US population (cost year 2011) found that compared to usual care, only educative documents sent by post achieved an ICER of less than $100,000 per QALY (considered as a "conventional cost-effectiveness threshold"), though recognized that cost-effectiveness, and perhaps even savings, could be achieved by adding the polypill to educative documents if its cost fell to less than $100 per patient month [43]. A later study in the UK (cost year 2014) found that when used in a post-MI secondary prevention setting, the polypill could prevent 47 cardiovascular events and 10 cardiovascular deaths per 1000 patient population, resulting in an ICER of £8,200 per QALY gained [11]. This suggests probable cost-effectiveness in the UK even taking into account the additional drug costs of the polypill (£463,500) which were partially offset by savings resulting from reduced cardiovascular events (£130,700) and patient management (£90,500) [11]. Furthermore, a recent report from the ISPOR 18th Annual European Congress suggested that when used as secondary prevention in the Spanish population, the polypill was dominant, with a total gain of 36 QUALYs and a 90.1% probability of the polypill being cost-effective at a willingness-to-pay threshold of €30,000 per QALY gained [44]. These results suggest that the polypill may be a cost-effective option for secondary prevention of CVD in some countries, though it should be noted that all of the above studies are based on assumptions and are yet to be demonstrated in the real world.

EXPERT OPINION

The polypill has been conclusively shown to improve patient adherence to CVD preventative medication, however the reported extent of this improvement has differed between studies. This is likely to be due to inconsistency in multiple variables such as setting, continent, type of polypill and the lack of standardised measure for quantifying adherence. The latter is of particular importance, owing to the majority of assessment approaches being subjective and highly-dependent on patient honesty. It has been suggested that analysis of drug metabolites is the most reliable method for assessing adherence [6], and development of this technique for low cost, easy application in future clinical trials would simplify comparisons and increase validity. Notwithstanding variations in amplitude, the effect of the polypill on adherence appears greater when used in a primary prevention setting and in patients who are not adherent at baseline, the latter of which have also been identified as a possible population standing to gain greater risk factor reduction from the polypill. This suggests such patients may be prime candidates for polypill therapy.

However, improved adherence has not consistently led to significantly greater degrees of efficacy compared to usual care. This is most likely the result of small sample sizes providing insufficient statistical power, coupled with trial lengths which do not extend adequately into the 1-2 year lag-phase preceding attainment of maximum SBP and LDL-C benefit on CVD medication [31, 32]. Ongoing, longer-term studies in larger patient populations will shed further light on the possible superiority of the polypill over usual care for risk factor reduction.

As expected, the polypill appears to have a comparable safety profile to its component parts and, contrary to previous concerns, it does not seem to negatively affect patient lifestyle behavior. However, despite good levels of patient acceptance and ease of prescription, it should be noted that this approach is not for everybody. The fixed nature of the polypill makes tailoring therapy to individual patient needs difficult, and practitioners may resist use on the basis of inflexibility. The production of more drug combinations at a greater range of doses will allow treatment of patients with contraindications to one or more polypill component (such as β-blockers in asthma patients) and provide more choice for practitioners, though in patients requiring aggressive, individualized therapy the polypill is unlikely to be adequate.

High levels of cost-effectiveness have been observed in a primary prevention setting, even in low-income countries. However, worldwide cost-effectiveness in a secondary prevention setting appears more dependent on polypill retail prices. Further studies and real-world data are necessary for additional clarification of efficacy and cost-effectiveness.

CONCLUSION

The polypill has demonstrated significant improvements in adherence accompanied by reduced SBP and LDL-C relative to usual care in larger-scale trials. This, coupled with a highly predictable safety profile, suggests that the polypill may be an effective alternative to polypharmacy for the prevention of cardiovascular events in both a primary and secondary setting. Ongoing studies will provide crucial longer-term evidence to supplement these findings.

AUTHOR CONTRIBITIONs

Peter Bramlage outlined the review, assembled the data, revised the manuscript for important intellectual content and approved the final version submitted. Helen Sims wrote the first draft of the manuscript, revised if based on the authors` comments and approved the final version to be submitted. Joan Minguet outlined the review, revised the manuscript for important intellectual content and approved the final version submitted. Carmen Ferrero revised the manuscript for important intellectual content and approved the final version submitted.

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TABLES

Table 1: Overview of most well-documented polypills for cardiovascular outcome prevention

Manufacturer	*Polypill name*	*Active components*	*Countries in which currently available*	*Studies in which used*
Dr. Reddy´s Laboratories, India	*Red Heart Pill™ 1*	*Aspirin (75mg), Atenolol (50mg), Lisinopril (10mg), Simvastatin (40mg)*	*Not yet available*	*UMPIRE, IMPACT, Kanyini-GAP, SPACE*
Dr. Reddy´s Laboratories, India	*Red Heart Pill™ 2*	*Aspirin (75mg), Hydrochlorothiazide (12.5mg), Lisinopril (10mg), Simvastatin (40mg)*	*Not yet available*	*UMPIRE, IMPACT, Kanyini-GAP, SPACE, PILL, TEMPUS*
Ferrer Internacional, Spain	*Trinomia®/ Sincronium®‡*	*Aspirin (100mg), Ramipril (2.5, 5 or 10mg), Atorvastatin (20mg)*	*Austria, Belgium, Bulgaria, Czech Republic, Finland, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Romania, Spain, Sweden*	*PROPS, SECURE*
Ferrer internacional, Spain	*Trinomia®*	*Aspirin (100mg), Ramipril (2.5. 5 or 10mg),Simvastatin (40mg)*	*South and Central America*	*FOCUS*
Cadila Pharmaceuticals Ltd. India	*Polycap®*	*Atenolol (50mg), Hydrochlorothiazide (12·5mg), Ramipril (5mg), Simvastatin (20mg), optional Aspirin (100mg)*	*India and Zambia*	*TIPS-1, TIPS-2, TIPS-3, HOPE-4*

	Polycap® DS	*Atenolol (100mg), Hydrochlorothiazide (25mg), Ramipril (10mg), Simvastatin (40mg)*		
Cipla, India	*Polypill‡*	*Amlodipine (2.5mg,) Losartan (25 mg), Hydrochlorthiazide (12.5 mg) and Simvastatin (40 mg)*	*India*	*Wald et al. 2012*
Alborz Darou Pharmaceutical Company, Iran	*PolyIran*	*Aspirin 81mg, Enalapril 5mg (or Valsartan 40mg), Atorvastatin 20mg and Hydrochlorothiazide 12.5mg*	*Iran*	*PolyIran*
AstraZeneca LP	*ATACAND HCT® 16-12.5**	*Candesartan (16mg), Hydrochlorothiazide (12.5mg)*	*33 countries worldwide*	*HOPE-3*

Legend: * not generally considered a "polypill" despite multiple components. ‡no official name given, ǂ in Germany named Sincronium® and manufactured by Hexal [8, 13, 17, 19-25, 33-38, 45-47]

Table 2: Important completed clinical trials with the polypill

	Countries included	Polypill	Clinical Trial Design	Patients	Study groups	Study duration	Primary Outcomes (method of assessment)
IMPACT [24]	New Zealand	Red Heart Pill™ version 1 or 2	Randomised, open label.	513 patients at high risk (>15%) of CVD.	Polypill vs usual care	Minimum 12 months	% of adherent patients (self-reported current use of antiplatelet, statin, and at least two blood pressure lowering drugs), LDL-C, and SBP at follow-up.
PILL [20]	Australia, Brazil, India, The Netherlands, New Zealand, UK , USA	Red Heart Pill ™ 2	Randomised, double-blind placebo-controlled.	378 patients with ≥7.5% estimated 5-year CVD risk.	Polypill vs placebo	12 weeks	Tolerability (proportion discontinued randomised therapy), LDL-C, and SBP at follow-up.
Wald et al 2012 [17]	UK	Cipla polypill[13]	Randomised placebo-controlled	86 patients aged 50 or over with no history of CVD	Polypill vs placebo	12 weeks	Reductions in LDL-C and SBP at 12 weeks.

			double-blind crossover.				
TIPS 1 [46]	India	Polycap™	Randomised, double-blind.	2053 individuals without CVD with one risk factor.	Polypill vs eight other usual care groups	16 weeks	LDL-C, SBP, heart rate, urinary 11-dehydrothromboxane B2, and rates of discontinuation at follow-up.
TIPS 2 [48]	India	Polycap™	Randomise[8]d double-blind 2x 2 factorial controlled.	518 patients with previous CVD or diabetes mellitus.	Single-dose polypill plus placebo or 2 polypill capsules plus K+	8 weeks	Effects on SBP, heart rate, serum lipids, serum and urinary K+, and tolerability at follow-up.
TEMPUS [21]	The Netherlands	Red Heart Pill ™ 2	Randomised, open, blinded end-point, three-period cross-over.	78 patients with established CVD.	Morning polypill vs evening polypill vs usual care	3-6 weeks per treatment period	% of adherent patients (microelectronic monitoring device), LDL-C and SBP on each regime.

FOCUS phase 2 [8]	Italy, Spain, Argentina, Paraguay	Trinomia®	Randomised, open-label, active-controlled, piggyback, parallel.	695 post-MI patients.	Polypill vs usual care	9 months	% of adherent patients (MAQ and pill count) at follow-up.
UMPIRE [23]	India and Europe (the UK, Ireland, and the Netherlands)	Red Heart Pill™ version 1 or 2	Randomised, open-label, blinded-end-point.	2004 patients with, or at high risk (>15%) of CVD.	Polypill vs usual care	24 months (minimum 12 months)	% of adherent patients (indicated medication taken on 4 of preceding 7 days), LDL-C and SBP at baseline and follow-up.
Kanyini-GAP [22]	Australia	Red Heart Pill™ version 1 or 2	Randomised, open-label.	623 patients with, or at high risk (>15%) of CVD.	Polypill vs usual care	34 months (minimum 12 months)	% of adherent patients (indicated medication taken on 4 of preceding 7 days) SBP and total cholesterol at baseline and follow-up.
SPACE [13]	As in IMPACT, UMPIRE and Kanyini-GAP	Red Heart Pill™ version 1 or 2	Meta-analysis	3140 patients from IMPACT, UMPIRE and Kanyini-GAP studies	Polypill vs usual care	12 months	% of adherent patients (self-reported current use on ≥4 days in the last week of antiplatelet, statin, and at least two blood

	pressure lowering drugs), LDL-C, and SBP at follow-up.

Legend: IMPACT, IMProving Adherence using Combination Therapy; PILL, Program to Improve Life and Longevity; TIPS, The Indian Polycap Study; TEMPUS, The Evening Versus Morning Polypill Utilization Study; FOCUS, Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention; UMPIRE Use of a Multidrug Pill In Reducing cardiovascular Events; Kanyini-GAP, Kanyini Guidelines Adherence with the Polypill; SPACE, Single Pill Against Cardiovascular Events; MI, myocardial infarction; CVD, cardiovascular disease; SBP, systolic blood pressure; LDL-C, LDL cholesterol, MAQ, Morisky-Green medication adherence questionnaire.

Table 3: Important ongoing clinical trials with the polypill

	Countries included	Polypill	Clinical Trial Design	Patients	Study groups	Study duration	Primary Outcomes	Expected completion
PROPS [36]	United Kingdom	Trinomia®	Multi-centre, randomised control	1222 patients post stroke / TIA aged ⩾55	Polypill vs usual care	6 months	Non-inferiority for SBP reduction	2018
TIPS-3 [33]	10 countries including Canada, Colombia, India, Malaysia, Phillipines, Tanzania.	Polycap DS®	2x2x2, factorial design, randomised, double blind, control.	5000 women (aged 60+) and men (aged 55+) without CVD	Polypill vs placebo, aspirin vs placebo and vitamin D vs placebo.	5 years	Major cardiovascular events, cardiovascular disease and risk of fracture.	March 2020
SECURE [37]	7 countries in Europe (Spain, Italy, Germany, France,	Trinomia®	Randomised, controlled,	3200 post-MI patients aged ⩾ 65	Polypill vs usual care	24 months	Incidence of cardiovascular outcomes.	October 2019

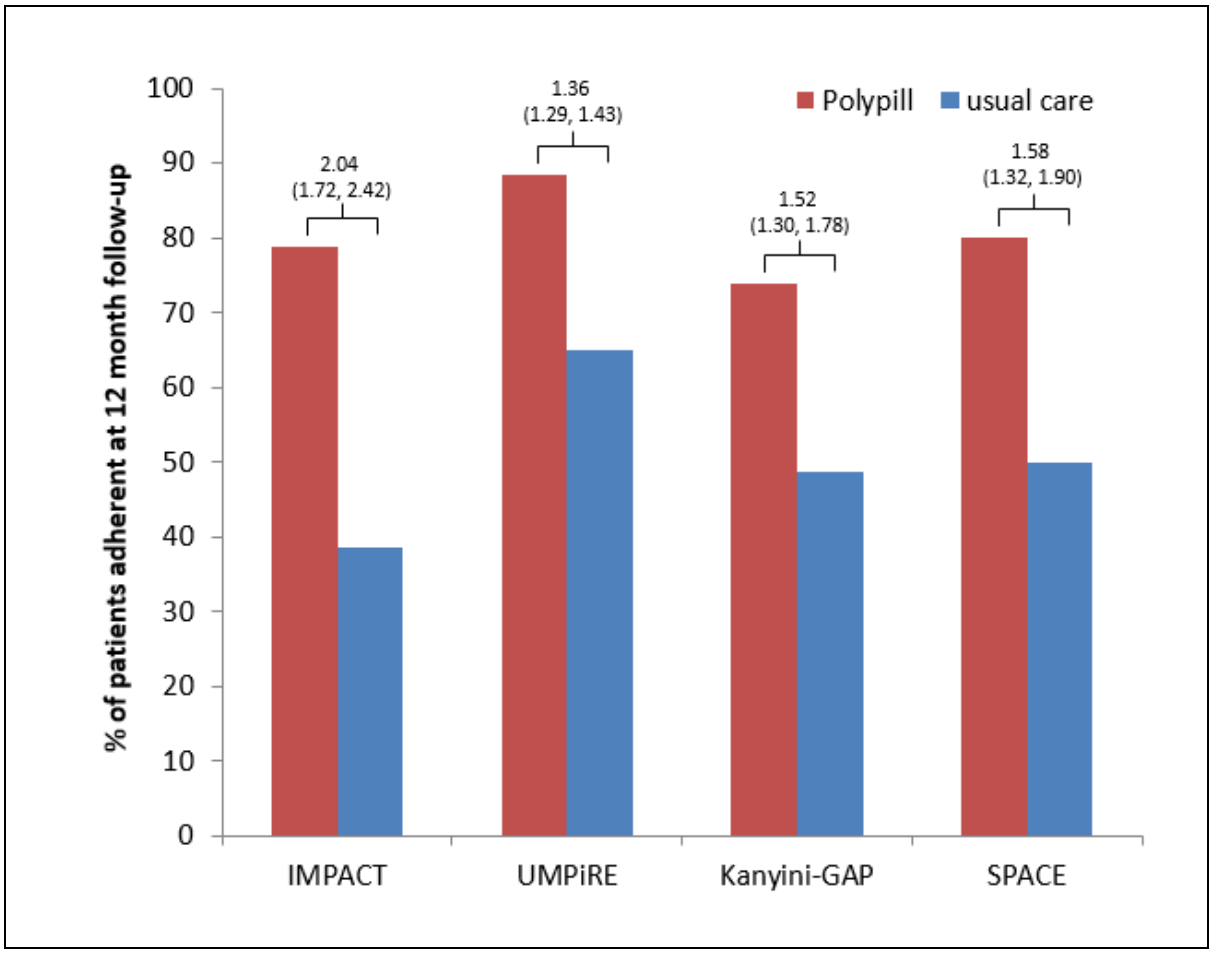
	Hungary, Poland and Czech Republic)		multi-centre, multinational					
HOPE-3 [34]	21 countries	ATACAND HCT® 16-12.5 plus rosuvastatin	Randomised, placebo-controlled trial	12,705 individuals aged >60 (women) or >55 (men), at medium risk of CVD	Rosuvastatin and candesartan/HCT vs candesartan/HCT alone vs rosuvastatin alone vs placebo.	5.7 years (average)	Effect on LDL-C, SBP and cardiovascular outcomes.	October 2015
HOPE-4 [35]	Canada, Colombia, Malaysia, Philippines, India, Argentina, South Africa,	Polycap® or Polycap® DS, both with and without aspirin (100mg).	Open-label, parallel cluster, randomised control	9500 patients (≥50) at risk of CVD	Education and support plus polypill compared to usual care.	6 years	Mean difference in change in Framingham Risk Score and cardiovascular outcomes.	August 2020

	Tanzania, and Rwanda.							
PolyIran [38]	Iran	PolyIran	Open cluster, randomised, control.	7000 patients aged >50 years, enrolled in the Golestan Cohort Study	Education and support plus polypill compared to usual or minimal care.	5 years	Time to first cardiovascular outcome.	April 2018

Legend: PROPS Preventative Role of a fixed dose combination Pill in Stroke; TIPS, The International Polycap Study; SECURE, Secondary Prevention of Cardiovascular Disease in the Elderly Trial; HOPE, Heart Outcomes Prevention and Evaluation; PolyIran, Prevention of Cardiovascular Disease in Middle-aged and Elderly Iranians Using a Single PolyPill; MI, myocardial infarction; CVD, cardiovascular disease; SBP, systolic blood pressure; LDL-C, LDL cholesterol, TIA, Transient ischemic attack; HCT, hydrochlorothiazide.

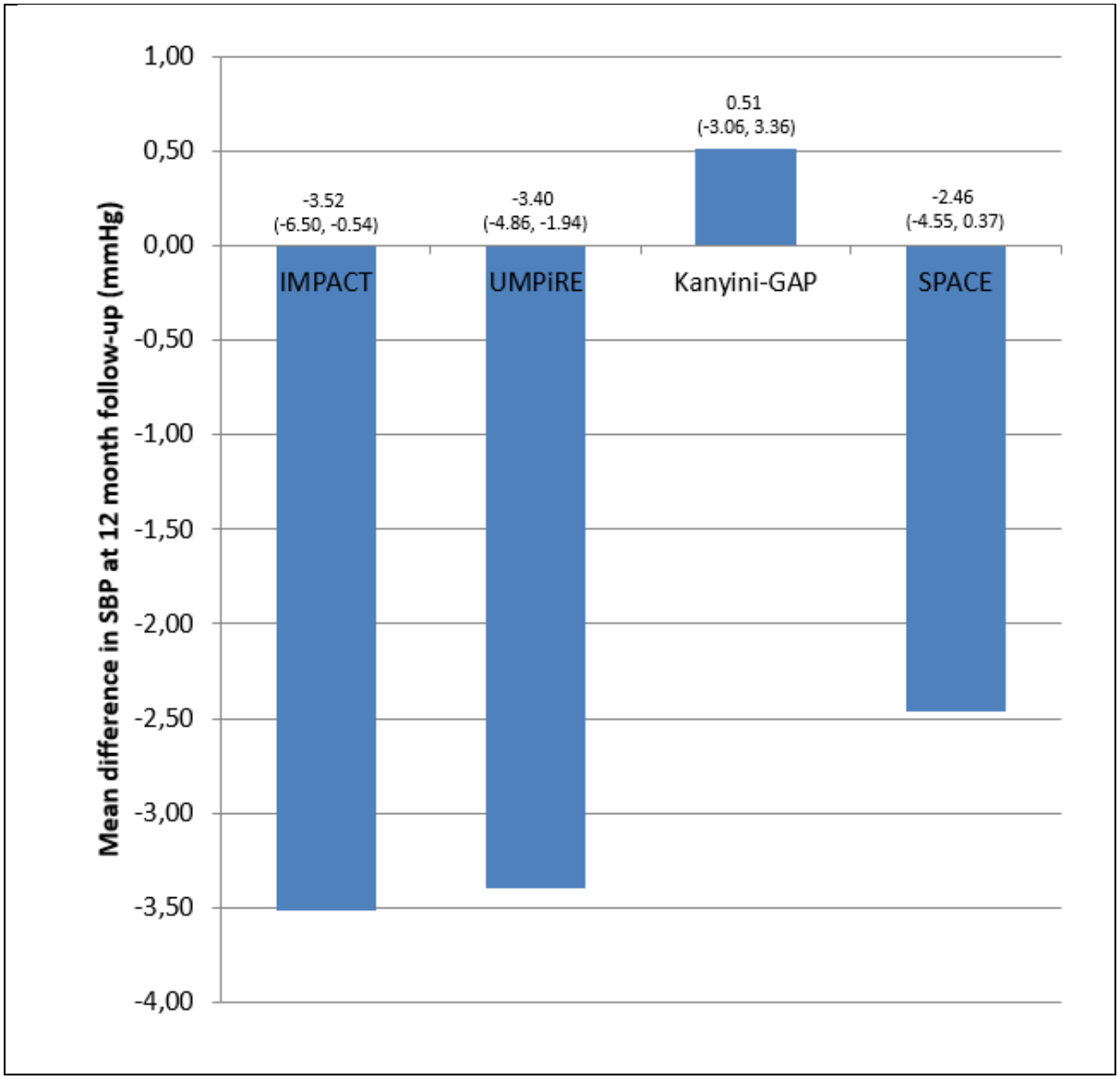
FIGURE LEGENDS

Figure 1: Proportion of adherent patients to the polypill or usual care at 12 months in the SPACE meta-analysis and component trials



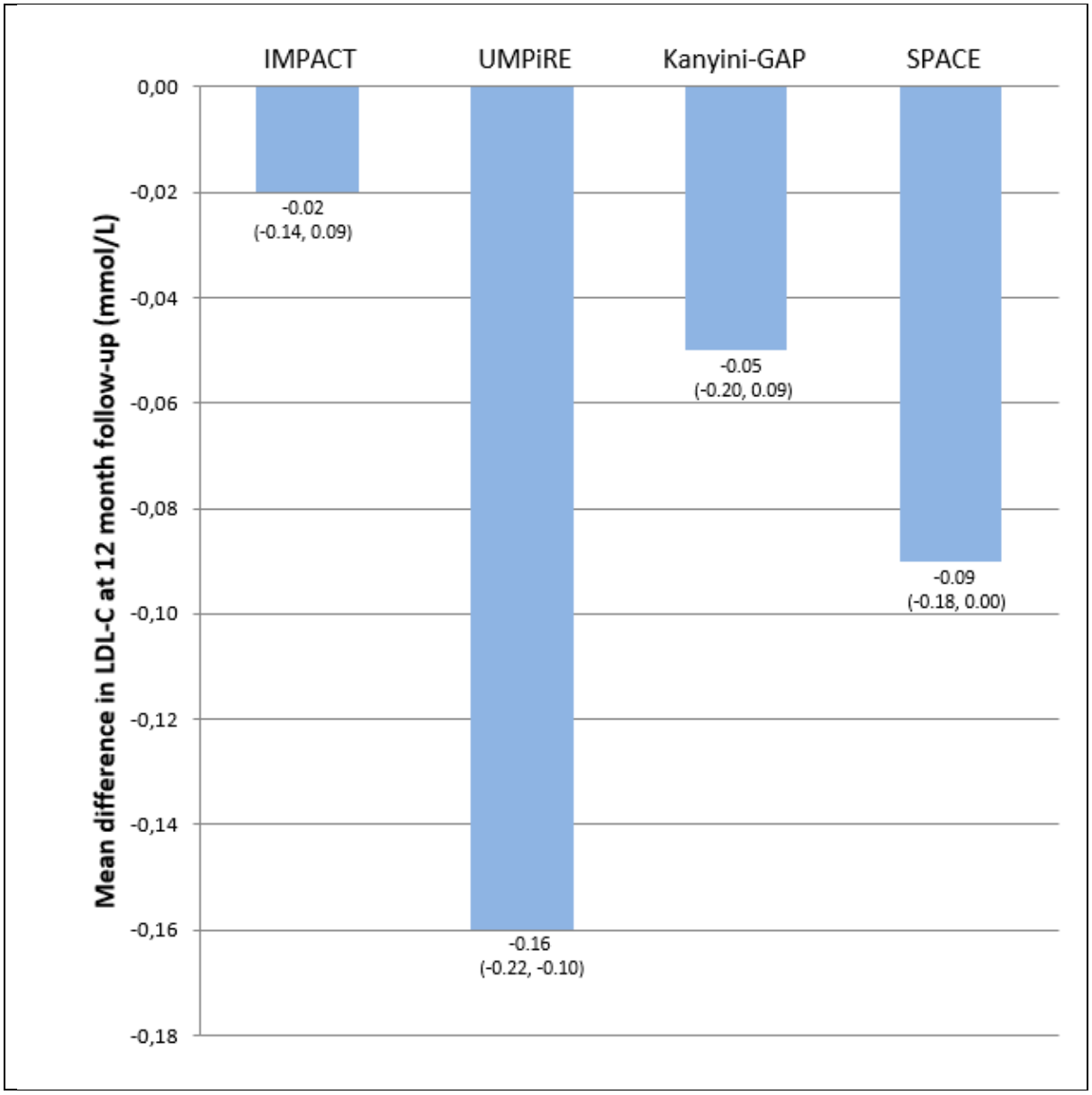
Legend: Values shown above each study are "risk ratio (95% confidence interval)" in favour of the polypill. All p values are **<0.001**. [13]

Figure 2: Mean difference in systolic blood pressure between polypill and usual care groups at 12 months in the SPACE meta-analysis and component trials.



Legend: Values shown above each study are "mean difference (95% confidence interval)" in favour of the polypill (IMPACT [**p=0.021**], UMPIRE [**p<0.001**] and SPACE [**p=0.021**]) or usual care (Kanyini-GAP [p=0.93]). [13]

Figure 3: Mean difference in LDL-cholesterol between polypill and usual care groups at 12 months in the SPACE meta-analysis and component trials.



Legend: Values shown above each study are "mean difference (95% confidence interval)" in favour of the polypill. P values are as follows: IMPACT p=0.67; UMPIRE **p<0.001**; Kanyini-GAP p=0.47; SPACE **p=0.04**. [13]