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Effectiveness of fixed dose combination medication ('polypills') compared with usual care in patients with cardiovascular disease or at high risk: A prospective, individual patient data meta-analysis of 3140 patients in six countries☆,☆☆

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ABSTRACT

Aims: To conduct a prospective, individual participant data (IPD) meta-analysis of randomised controlled trials comparing a polypill-based approach with usual care in high risk individuals.
Methods and results: Three trials comparing polypill-based care with usual care in individuals with CVD or high calculated cardiovascular risk contributed IPD. Primary outcomes were self-reported adherence to combination therapy (anti-platelet, statin and ≥two blood pressure (BP) lowering agents), and difference in mean systolic BP (SBP) and LDL-cholesterol at 12 months. Analyses used random effects models. Among 3140 patients from Australia, England, India, Ireland, New Zealand and The Netherlands (75% male, mean age 62 years), median follow-up was 15 months. At baseline, 84%, 87% and 61% respectively were taking a statin, anti-platelet agent and at least two BP lowering agents. At 12 months, compared to usual care, participants in the polypill arm had higher adherence to combination therapy (80% vs. 50%, RR 1.58; 95% CI, 1.32 to 1.90; $p < 0.001$), lower SBP (−2.5 mmHg; 95% CI, −4.5 to −0.4; $p = 0.02$) and lower LDL-cholesterol (−0.1 mmol/L; 95% CI, −0.2 to 0.0; $p = 0.04$). Baseline treatment levels were a major effect modifier for adherence and SBP (p-homog <0.0001 and 0.02 respectively) with greatest improvements seen among those under-treated at baseline.
Conclusions: Polypill therapy significantly improved adherence, SBP and LDL-cholesterol in high risk patients compared with usual care, especially among those who were under-treated at baseline.

1. Introduction

In high income countries, only around half of people with established cardiovascular disease (CVD) take guidelines-recommended anti-platelet, blood pressure lowering and cholesterol lowering therapies long-term [1]. In low income countries this proportion is as low as 5% [1]. Medication adherence is related to many factors, including availability, affordability, regimen complexity and number of pills. The combination of multiple classes of low cost generic CVD preventive medications

☆ The project is registered with the Australian New Zealand Clinical Trial Registry: ACTRN12612000980831

☆☆ **Translational perspective**: These results showed that polypill-based care in patients at high risk of CVD improved adherence and risk factor levels across a wide range of patient groups. There was little evidence of net benefit for those already well treated but there is likely to be a significant net benefit for those undertreated.

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into one pill (a "polypill") has been proposed as one way of overcoming these barriers [2,3]. Recent trials have indicated that such treatment can improve adherence among patients with CVD or similarly high risk [4–7]. However, there is uncertainty about the consistency of these findings across different patient groups, across different health care systems in which usual care may vary considerably and with different levels of out-of-pocket medication payments. Furthermore, there are theoretical risks associated with such treatment, including the possibility of poorer outcomes in patients switched to polypills containing off-patent medications (especially if switched from more potent statins) and neglect of lifestyle factors whilst taking a polypill.

To address these issues, we conducted a prospective, individual participant data (IPD) meta-analysis of randomised controlled trials comparing a polypill-based approach with usual care in high risk individuals.

2. Methods

Three trials were collaboratively planned, conducted and analysed, based on the same protocol, with minor regional adaptations: UMPIRE [6], with participants from the United Kingdom, Ireland, The Netherlands, and India; Kanyini-GAP conducted in Australia [4] and IMPACT conducted in New Zealand [5]. A prospective IPD meta-analysis was also registered with the Australian New Zealand Clinical Trial Registry: ACTRN12612000980831 with a protocol and pre-specified data analysis plan published [8]. Further information can be found at www.spacecollaboration.org.

2.1. Trial designs

All three trials used a randomised, open label, blinded endpoint design, comparing polypill-based care with usual care in individuals with established CVD or at high risk thereof [9–11].

CVD events were verified by blinded adjudication, and hardcopy printouts from calibrated BP monitors and laboratory blood chemistry reports were used to monitor data quality.

2.2. Study population

Key inclusion criteria were: established atherothrombotic cardiovascular disease (CVD), or a Framingham-based calculated 5-year CVD risk of ≥15% [12]. Participants also had to have indications for all the components of at least one polypill, according to the patient's regular physician. In the UMPIRE Trial, half the participants were from India and in the IMPACT and Kanyini-GAP trials, half the participants were Indigenous peoples.

Exclusion criteria for all trials included: any contraindication to components of the polypill, being clinically inappropriate according to the treating physician to change the patient's cardiovascular medication regimen and the patient unlikely to complete the trial, including trial visits. The IMPACT trial also specifically excluded patients with chronic heart failure, active stomach or duodenal ulcers, haemorrhagic stroke or taking an oral anti-coagulant.

2.3. Randomisation

Participants were randomised 1:1 by central computer-based randomisation to polypill-based care or to continued usual care. Randomisation was stratified by site (UMPIRE and Kanyini-GAP) or Primary Health Organisation (IMPACT), presence of CVD at baseline (all trials), Indigenous status (IMPACT and Kanyini-GAP) and whether participants were taking combination therapy (anti-platelet, statin and ≥2 blood pressure (BP) lowering agents) at baseline (IMPACT and Kanyini-GAP).

2.4. Study medication

Two versions of the polypill (Red Heart Pill — manufactured and supplied by Dr. Reddy's Laboratories, Hyderabad, India) were available. The choice of polypill version was made by the patient's regular physician, who indicated prior to randomisation the version of the polypill they would use for that patient if they were randomised to the polypill group. The polypill versions were:

Polypill version 1 (V1): aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, atenolol 50 mg;

polypill version 2 (V2): aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg.

Participants' physicians were encouraged to provide usual care according to current guidelines for individuals at high CVD risk. Both polypill and usual care groups were managed by the patient's regular physician or according to usual clinical pathways. In patients randomised to the polypill, additional anti-platelet, statin and BP lowering medication could be prescribed by their physicians.

2.5. Outcomes

Primary outcomes were:

1. Self-reported adherence to combination therapy (defined as anti-platelet, statin and at least two BP lowering drugs) on ≥4 days in the last week at 12 months;
2. change in systolic BP (SBP) from baseline to 12 months; and
3. change in LDL cholesterol from baseline to 12 months.

For the measurement of adherence the World Health Organisation recommends 'utilisation of a multi-method approach that combines feasible self-reporting and reasonable objective measures' [13] hence the choice of a combined outcome including a subjective measure and 2 objective biological co-primary outcomes (Fig. 1).

These primary outcomes were also evaluated at the end of follow-up. Sensitivity analyses were also conducted which included an alternate definition of adherence as taking combination therapy 7 out of 7 days in the past week and at least 1 day out of 7 in the past week to see if this would change the primary outcome results. Change from baseline to 12 months in adherence to each of the separate components of therapy (i.e. anti-platelet, statin and ≥2 blood pressure lowering drugs) was also examined.

Secondary outcomes at 12 months are described in Table 2 as previously published [8].

2.6. Statistical methods

Primary and secondary outcomes analyses were performed on the combined dataset using preferred one-stage meta-analyses (i.e. individual patient data were pooled and then models run on the combined dataset) [14]. For BP, cholesterol and other continuous outcomes, the primary analyses consisted of a linear mixed model with the 12-month value as the outcome, the baseline value and the treatment arm as fixed effects, and a random trial intercept and random trial-by-treatment interaction. For adherence and other dichotomous outcomes, a log-binomial regression with a fixed treatment effect, a random trial intercept and random trial-by-treatment interaction was used. Where convergence occurred, the effect of each trial was considered fixed instead of random. Sensitivity analyses included fixed-effect models and traditional two-stage approaches using both random and fixed effects meta-analyses.

Time-to-event analyses were performed using Cox models using a general frailty model with a fixed treatment effect, a random intercept per trial and a random trial-by-treatment interaction. Subgroup analyses were performed by adding a fixed interaction between the treatment effect and the subgroup of interest. Pre-specified subgroups were age, sex, presence or absence of established disease, country and intention to prescribe Red Heart Pill V1 or V2. Pre-specified covariates for adjusted analyses included age, sex, and presence or absence of established disease, country and version of the Red Heart Pill. An additional non-prespecified subgroup analysis examined effect by level of adherence to 'combination treatment' at baseline as this was shown to be a significant effect modifier in each of the individual trials.

Two analyses which were not pre-specified were conducted, in light of possible concerns about the safety of polypill-based care [15]. First, it has been suggested that a polypill treatment strategy may lead to neglect of lifestyle measures. Additional post-hoc analyses were conducted to assess safety among patients switched from more potent statins [16] (atorvastatin ≥20 mg, rosuvastatin ≥10 mg) to polypill-based care. All analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

Data were available for all 3140 patients randomised within the 3 trials. Median follow-up overall was 15 months (inter-quartile range: 12 to 21). Intervention and control groups were similar at baseline (Table 1), 75% were male, mean age was 62 years and 76% had established CVD. At baseline, treatment rates were 84% for statin therapy, 87% for antiplatelet therapy, 91% were taking at least one BP lowering agent and 61% were taking two or more BP lowering agents. Overall, 55% were adhering to combination therapy at baseline.

Moderate to high levels of statistical heterogeneity was observed with I [2] percentage estimates for adherence, SBP and LDL cholesterol of 90.5%, 51.0% and 59.5% respectively. Fixed effects analyses were also done as a sensitivity analysis.

3.1. Primary outcomes of adherence, SBP and LDL cholesterol

At 12 months, 80% of participants in the polypill arm reported adherence to combination therapy compared with 50% in the usual care arm (RR 1.58; 95% CI: 1.32 to 1.90; $p < 0.0001$ — Table 1). Fixed effects model results for adherence were similar: 78% compared with 54%, respectively (RR 1.43; 95% CI: 1.36 to 1.51; $p < 0.0001$). Mean SBP in the polypill arm was lower than in the usual care arm (−2.5 mmHg; 95% CI: −4.5 to −0.4, $p = 0.02$). A reduction in LDL

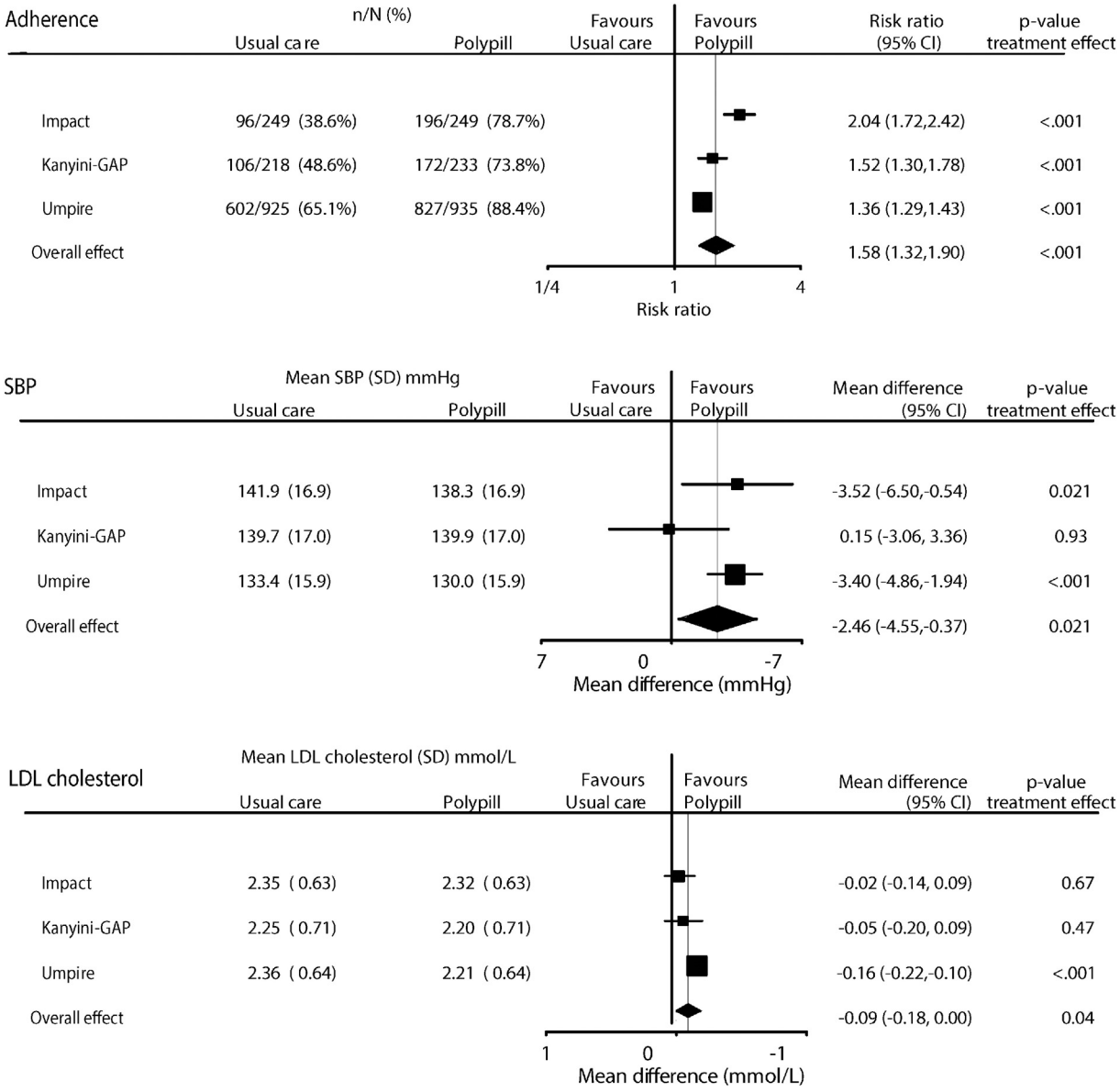

Fig. 1. Primary outcomes at 12 months by trial and overall.

cholesterol in the polypill arm was also observed compared with usual care (−0.09 mmol/L; 95% CI: −0.18 to 0.00; p = 0.04). Fixed effects model results for SBP and LDL cholesterol were −2.8 mmHg (95% CI: −4.1 to −1.6, p < 0.0001) and −0.12 mmol/L (95% CI: −0.17 to −0.07, p < 0.0001), respectively. When adjustments were made for pre-specified covariates (age, sex, presence of established CVD), the outcomes were attenuated for adherence (RR 1.33; 95% CI: 1.12 to 1.58; p = 0.001), but the mean differences in SBP or LDL cholesterol were almost identical: −2.9 mmHg, (95% CI: −4.1 to −1.7, p < 0.0001) and −0.09 mmol/L (95% CI: −0.18 to −0.01, p = 0.03), respectively.

3.2. Subgroup analyses of primary outcomes

Pre-specified subgroup analysis for the adherence outcome (Fig. 2) showed statistical heterogeneity across subgroups by age, country, baseline adherence to combination therapy, established CVD and polypill version. This heterogeneity was largest for the subgroup defined by baseline adherence, with combination therapy use improving from 17% to 74% (RR = 4.46, 95% CI: 3.72 to 5.36) for those non-adherent at baseline, but only 86% to 90% (RR = 1.04, 95% CI: 1.01 to 1.07) for those adherent at baseline. For SBP only baseline adherence was shown to be a significant effect modifier (p = 0.02 for the interaction). For LDL cholesterol, the effect size changed significantly by age, country and established CVD.

Fig. 3 shows that at one month after randomisation, the proportion receiving combination therapy increased to 80–95% for all patients in the polypill group irrespective of the number of treatments being taken at baseline. In the usual care group there was also a moderate increase in treatment rates from 0 to 1 month.

There was some early drop-off in treatment adherence in the polypill group, especially among those under-treated at baseline. However combination therapy treatment rates remained higher in the polypill group at all times, and at 18 months this improvement was greatest in those receiving least treatment at baseline.

3.3. Additional analyses for primary outcomes

At the end of study (median duration of follow up 15 months) effects were largely unchanged for adherence (76% vs. 49%; RR 1.53, 95% CI: 1.3–1.82); p < 0.0001), mean change in SBP (−2.7 mmHg, 95% CI: −3.9 to −1.5; p < 0.0001) and mean change in LDL cholesterol

Table 1
Baseline characteristics.

Baseline characteristic	Polypill N = 1569	Usual care N = 1571
Age, years (SD)	62.3 (10.6)	62.0 (10.9)
Female, n (%)	398 (25.4%)	381 (24.3%)
Heart rate, bpm (SD)	71.5 (14.6)	70.9 (14.2)
BMI, Kg/m2 (SD)	28.8 (6.0)	28.9 (6.2)
Waist, cm (SD)	100.9 (14.1)	101.3 (14.0)
Current smoker, n (%)	312 (19.9%)	322 (20.5%)
Systolic BP, mmHg (SD)	139.2 (20.8)	139.8 (21.0)
Diastolic BP, mmHg (SD)	79.0 (12.1)	79.5 (11.9)
Total cholesterol, mmol/L (SD)	4.2 (1.0)	4.3 (1.3)
HDL cholesterol, (mmol/L (SD)	1.1 (0.3)	1.1 (0.3)
LDL cholesterol derived, mmol/L (SD)	2.4 (0.9)	2.4 (0.9)
Triglycerides, mmol/L (SD)	1.6 (1.1)	1.6 (1.0)
Creatinine, μmol/L (SD)	88.1 (30.3)	88.6 (25.0)
History of coronary heart disease, n (%)	1021 (65.1%)	1025 (65.3%)
History of atrial fibrillation, n (%)	35 (2.2%)	43 (2.7%)
History of cerebrovascular disease, n (%)	216 (13.8%)	231 (14.7%)
History of peripheral vascular disease, n (%)	92 (5.9%)	70 (4.5%)
No history of symptomatic cardiovascular disease, n (%)	377 (24%)	367 (23%)
Diabetes mellitus, n (%)	581 (37.0%)	542 (34.5%)
Family history of premature heart disease or ischaemic stroke, n (%)	400 (25.7%)	419 (26.9%)
Intention to allocate to Polypill V1 or Polypill V2[a], n (%)		
Polypill V1	852 (54.3%)	866(55.2%)
Polypill V2	717 (45.7%)	702 (44.8%)

[a] V1 = aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, atenolol 50 mg; V2 = aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg.

(−0.07 mmol/L, 95% CI: −0.18 to 0.04; p = 0.24). Changing the definition of adherence by number of days the medication was taken in the previous week made little difference to estimates of self-reported adherence to combination therapy. The effect estimate for 7 out of 7 days (73% vs. 44%, RR 1.64, 95% CI: 1.39–1.94, p < 0.0001) was similar to that for at least 1 day out of 7 (80% vs. 51%, RR 1.57, 95% CI: 1.29–1.91, p < 0.0001). Medication use at 12 months was significantly improved for all categories of medications (Fig. 3, panels A–C).

3.4. Secondary outcomes

When adherence was re-defined as taking statin, antiplatelet and at least one BP lowering drug, the polypill-based strategy remained superior at 12 months (Table 2) and at the end of follow-up although the effect size was smaller than for the primary endpoint. There were no significant differences between the two groups for mean change in diastolic BP, total cholesterol, HDL cholesterol, triglycerides, creatinine or quality of life scores over 12 months. A moderate improvement in non-HDL cholesterol over 12 months was observed in the polypill compared with the usual care group.

Overall, 167 participants had a fatal or non-fatal cardiovascular endpoint event during follow-up (92 in the polypill group and 75 in the usual care group; RR 1.23 [0.91 to 1.65]; p = 0.18, Table 2). Fifty-four participants died from all causes during follow-up (25 in the polypill arm and 29 in the usual care arm; RR 0.86 [0.51 to 1.47]; p = 0.6) with significantly fewer deaths ascribed to non-cardiovascular causes in the polypill group and no significant difference in deaths ascribed to cardiovascular causes.

For the pre-specified endpoint reflecting new onset diabetes (new prescription of glucose lowering medication or fasting blood glucose >7 mmol/L during follow-up among those without diabetes at baseline), there was no difference between groups (RR = 0.87, 0.27 to 2.87, p = 0.83).

3.5. Reasons for stopping treatment

Four hundred and forty-six (30%) participants in the polypill arm permanently discontinued the polypill during follow-up (Table 3) with the majority transferring back onto individual medications. Of those stopping polypill treatment, the most common reasons provided were possible side effects (35%), most commonly cough, followed by doctor's advice (23%). Twenty percent of participants stopped of their own accord. No comparable data were collected in the usual care group beyond data required to determine the specified endpoints for self-reported adherence.

3.6. Serious adverse events (SAEs)

The number of participants with at least one SAE in the polypill arm was 360 (22.9%) whereas in usual care it was 316 (20.1%), RR 1.12 (0.99 to 1.27, p = 0.07) (Table 4). In the polypill arm more SAEs were reported as "medically important" (145 vs. 115, p = 0.04) but no significant excess of other SAEs (i.e. fatal, life-threatening, leading to hospitalisation). SAEs by 25 different MedDRA [17] system organ class categories were not significantly different between arms except for miscellaneous vascular disorders (35 vs. 17; of which hypotension accounted for 11 vs. 0) and breast and reproductive disorders (6 vs. 17 events, of which prostate issues including benign prostatic hyperplasia, accounted for 3 vs. 10). There was a numerical excess of reported SAEs at months 1 and 6 in the polypill arm (data not shown).

3.7. Additional safety analyses

We found no evidence to support the concern that use of a polypill-based strategy reduces healthy lifestyle behaviour: mean differences in BMI and waist circumference were 0 kg/m^2 (−0.2 to 0.2; p = 0.76) and 0.2 cm (−0.2 to 0.6; p = 0.42) respectively. The RR of current smoking at 12 months was 0.94 (0.75 to 1.16; p = 0.54). In the largest trial (UMPIRE), self-reported intensive physical activity levels were not reduced, and moderate activity levels were increased [6].

Among the 724 participants taking a more potent statin at baseline (almost all of whom were taking atorvastatin ≥20 mg or rosuvastatin ≥10 mg), allocation to a polypill did not lead to a deterioration in LDL control at 12 months (LDL difference 0.05; −0.05 to 0.14 mmol/l).

4. Discussion

4.1. Summary of findings

This individual participant data meta-analysis found that polypill-based care significantly improved adherence to recommended CVD

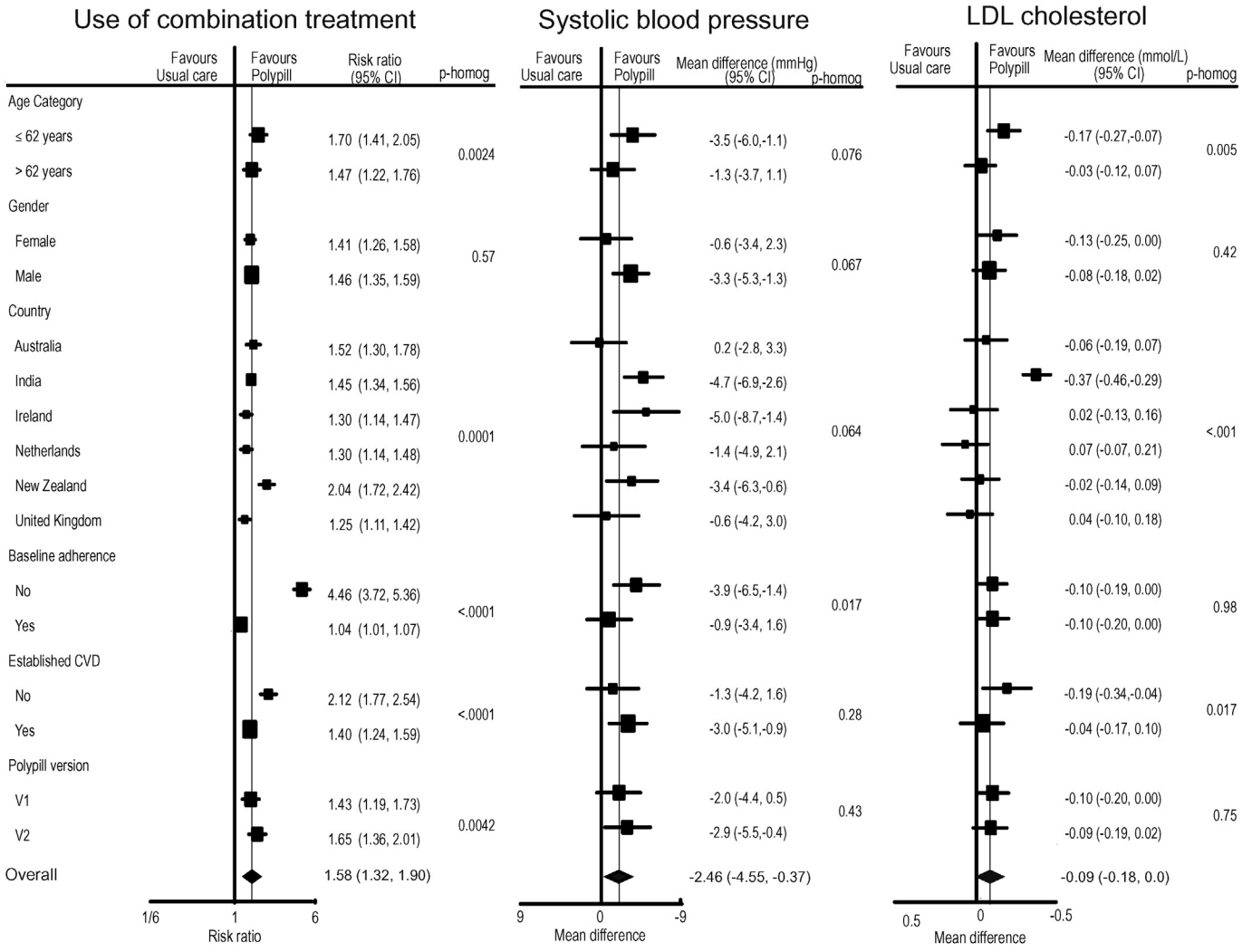

Fig. 2. Primary outcomes, by pre-specified subgroups.

medications, SBP and LDL cholesterol levels. The effects were broadly consistent across different subgroups with some heterogeneity noted; the most sizeable benefits in adherence and SBP were observed in the subgroup not taking full combination treatment at baseline. There were significantly increased numbers of medically important side effects reported, with no difference in CVD events or mortality. No adverse effects on objective measures of healthy lifestyle activities including BMI, waist circumference and smoking status were observed. Additionally allocation to the polypill arm did not result in any deterioration in LDL control at 12 months. The most likely explanation for this is that the improvement in adherence seen in the polypill arm offset any potential negative effect of randomisation to a less potent statin.

The apparent discrepancy between a large improvement in adherence and modest improvements in risk factor levels is likely due to two factors. Firstly, usual care among participants involved atypically high treatment rates [1]. At baseline, statins were already being used by 85% of patients and 90% of individuals were already taking some blood pressure lowering drug. Thus there was relatively little room for improvement. Secondly, adherence encompassed a composite definition of adherence to statin, anti-platelet and ≥2 BP lowering agents. Thus (as demonstrated in Fig. 3), the overall improvement in adherence was the sum of a modest improvement in combination BP lowering therapy and small improvements in adherence to statins and anti-platelet agents.

There was a borderline excess of the number of patients reporting one or more SAEs (23% vs. 20%, $p = 0.07$) in the polypill arm, with a numerical excess at the 1 and 6 month visits. This could partly be due to a lower threshold for reporting events in the polypill group in this unblinded trial, as there was a numerical excess in 18 of 24 diverse SAE categories; and hypotension was reported for 11 patients in the polypill group but none in the usual care group, whereas hypotension is typically reported in the placebo group of placebo-controlled trials [18]. Nonetheless, when switching people from stable treatment regimens, often with an increase in the number and types of medications being taken, a real increase in adverse events might be expected. These analyses suggest that any increase is modest in size and occurs within 6 months of the switch. A greater variety of polypill versions, for example a formulation with an angiotensin receptor blocker rather than an ACE inhibitor, or a range of dose combinations, would likely reduce the incidence of side effects, and also reduce the number of people stopping polypill therapy once started.

Our analysis did not show a reduction in cardiovascular events. This is not unexpected given the relatively small number of events overall, the small absolute improvements in risk factors (2.5/1.2 mmHg, 0.1 mmol/l LDL, and 4% more taking antiplatelet therapy) due to the active comparator in usual care, and the relatively short follow-up of 15 months (previous trials have shown a lag time of 1–2 years before the onset of benefits from BP and cholesterol lowering [19,20]). The required sample size to detect a relative risk

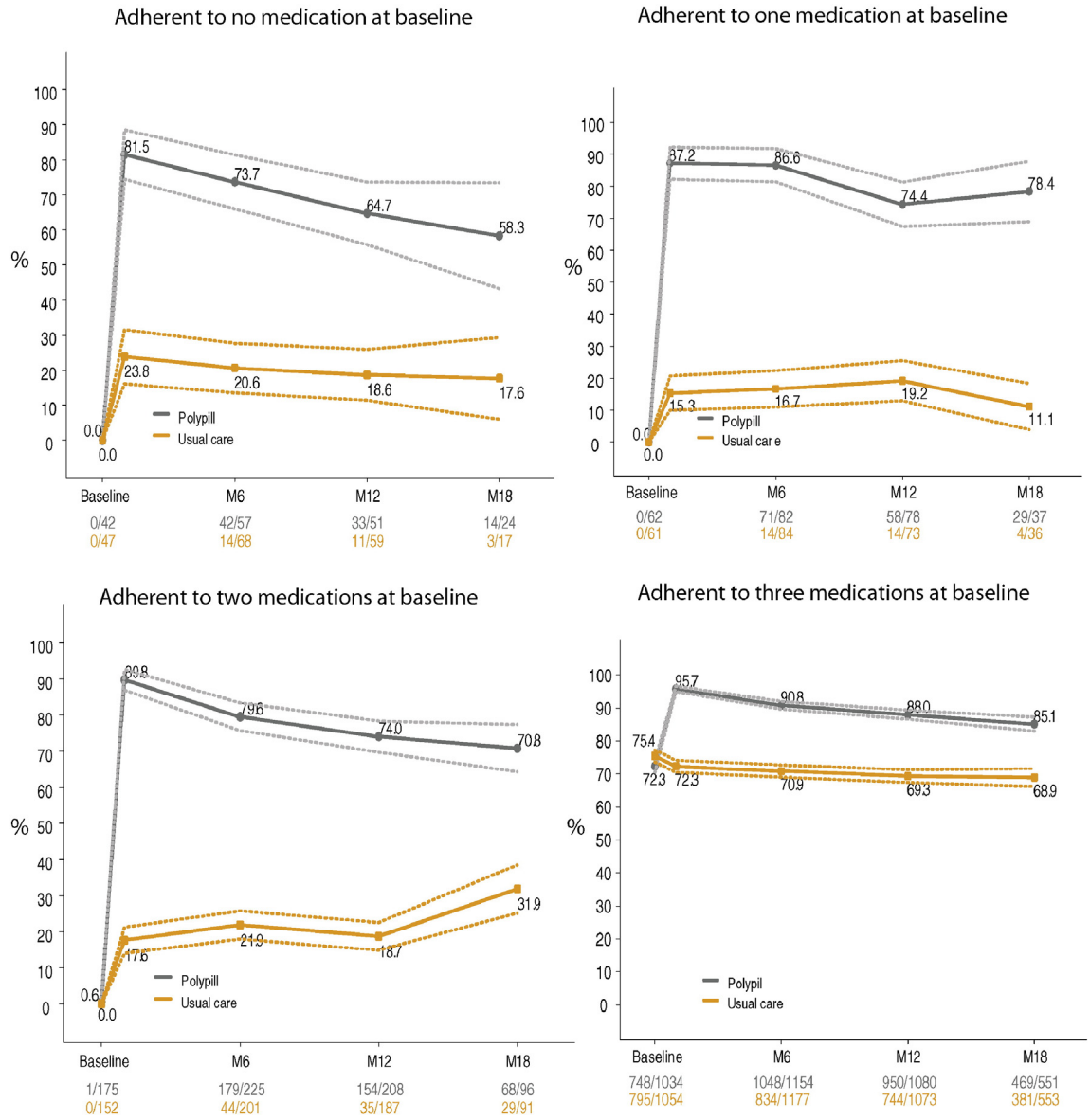

Fig. 3. Adherence to individual CVD preventive treatments by visit (A, B and C) and adherence to combination therapy (defined as statin, anti-platelet and ≥2 BP lowering medications) by varying adherence at baseline (D, E and F).

reduction of 15% (assuming a CV event rate of 3% per year in the usual care group, 1.5 years follow-up, α of 0.05 and 80% power) is 27,000 patients. Even with a combined CV events outcome, the number of patients needed to detect such a RRR far exceeds the number of patients included in this meta-analysis.

Other explanations include the play of chance, an unexplained harmful effect of polypill allocation, or a bias in reporting of events. This bias could have arisen as a result of the open label nature of the trials, and is suggested by the SAE reporting patterns noted above and the significant reduction in deaths ascribed to non-cardiovascular causes in the polypill group. There may have been a tendency to ascribe deaths to a cardiovascular cause in the polypill group. Nonetheless, among patients already receiving full treatment, it seems unlikely that switching to a polypill will achieve clinically relevant reductions in cardiovascular events. However, among those who are not receiving antiplatelet, statin and blood pressure lowering, an eventual reduction in cardiovascular events can reasonably be expected, given the conclusive evidence that some treatment is better than none for all drugs included in these polypills [21–23].

4.2. Strengths and limitations

Strengths of this meta-analysis are the use of individual patient data, the number of participants, length of follow-up, completeness of data collection and the pragmatic nature of the study design. Self-reported adherence was supported by the co-primary endpoints of changes in BP and cholesterol. Furthermore, the IMPACT trial compared prescribing rates from national databases and found high correlation with patient self-reported adherence [5]. In particular, this meta-analysis provides the most reliable assessment to date of the consistency of findings across different patient subpopulations and clinical settings.

Limitations include the fact that the studies were unblinded, raising the possibility of differential treatment, investigation, diagnosis or reporting of events within the trial setting. Despite efforts to recruit disadvantaged populations, the trial populations were unusually well treated [1]. This may limit the generalisability of results, as does the fact that trial volunteers may well be atypical, although these aspects tend to an underestimation of the effect of the intervention. Finally, there was insufficient power to assess effects on major morbidity and

Table 2
Secondary outcomes.

Outcome[a]	Polypill N = 1569	Usual care N = 1571	Treatment effect	Treatment effect p-value
	N (%)	N (%)	*Relative risk* (95% CI)	
Self-reported use of antiplatelet, statin and ≥1 BP lowering therapy	(84%)	(76%)	1.11 (1.07;1.14)	<0.0001
	Mean (SD)	Mean (SD)	*Mean Difference* (95% CI)	
Diastolic BP (mmHg)	77.3 (2.7)	78.5 (2.7)	−1.2 (−3.2;0.8)	0.25
Total cholesterol (mmol/L)	4.18 (0.08)	4.24 (0.08)	−0.07 (−0.17;0.04)	0.24
HDL cholesterol (mmol/L)	1.16 (0.02)	1.16 (0.02)	0.00 (−0.01;0.01)	0.97
Non-HDL cholesterol (mmol/L)	3.00 (0.07)	3.09 (0.07)	−0.09 (−0.18;0.00)	0.04
Triglycerides (mmol/L)	1.68 (0.05)	1.70 (0.05)	−0.02 (−0.08;0.03)	0.42
Creatinine (umol/L)	92.43 (1.25)	91.22 (1.27)	1.21 (−0.38;2.79)	0.14
Quality of life: EQUK	0.83 (0.02)	0.83 (0.02)	−0.01 (−0.04;0.02)	0.62
Quality of life: VAS score	74.79 (2.4)	75.79 (2.4)	−1.00 (−3.65;1.66)	0.46
	N (%)	N (%)	*Relative risk* (95% CI)	
All-cause mortality	25 (1.6%)	29 (1.8%)	0.86 (0.51;1.47)	0.59
Cardiovascular mortality	18 (1.1%)	12 (0.8%)	1.50 (0.73;3.10)	0.27
Non-cardiovascular mortality	7 (0.4%)	17 (1.1%)	0.41 (0.17;0.99)	0.05
All cardiovascular events	92 (5.9%)	75 (4.8%)	1.23 (0.91;1.65)	0.18
All coronary heart disease events	58 (3.7%)	50 (3.2%)	1.16 (0.80;1.68)	0.43
All heart failure events	7 (0.4%)	4 (0.3%)	1.35 (0.16;11.43)	0.78
All cerebrovascular events	17 (1.1%)	11 (0.7%)	1.52 (0.53;4.34)	0.43
All peripheral arterial events	19 (1.2%)	16 (1.0%)	1.33 (0.55;3.23)	0.52
Cardiovascular events excluding procedures	61 (3.9%)	43 (2.7%)	1.42 (0.97;2.08)	0.07

[a] All outcomes at 12 months except mortality and CV outcomes which were during all follow-up.

mortality. However, given the proven effects of each component on major clinical outcomes one could reasonably propose such data are not critical prior to implementation of polypill-based care in undertreated patients.

4.3. Research in context

The only randomised trial to compare long term use of a polypill versus usual care in high-risk primary prevention was conducted in Sri Lanka in 216 patients without established disease, but with a 10-year cardiovascular disease risk of at least 20% [24]. This study did not show any significant improvement in adherence, systolic blood pressure or total cholesterol with the polypill. However, the authors of this open-label trial noted that the 'usual care' group received an unusually high level of care following randomisation.

The FOCUS study is the only other trial that has investigated the long-term effect of polypill-based care versus usual care in a secondary prevention population [7]. This study was conducted in Argentina, Brazil, Italy, Paraguay and Spain and recruited 698 patients with previous myocardial infarction, followed for an average of 9 months. Participants were randomised to a polypill containing aspirin, simvastatin and ramipril, or to a control group with the same medicines as separate pills. The primary outcome of self-reported adherence was consistent with the findings from this meta-analysis, showing an improvement from 41% in participants taking individual medications to 51% in the polypill group (p = 0.02).

Table 3
Reasons for permanently discontinuing the polypill (N = 446).

Reason	n (%)
Side effects	160 (36)
Cough	66 (15)
GI upset	8 (2)
Other possible side effects	86 (19)
Advice of doctor	105 (24)
Patient choice	85 (19)
Due to serious adverse event (SAE)	49 (11)
Other	24 (5)
Uncontrolled risk factors	5 (1)
Unknown	18(4)

TIPS2, an 8 week study of 519 people with previous vascular disease or diabetes, showed that a double dose polypill reduced BP and LDL cholesterol to a greater extent than a single dose polypill, with comparable side effects [25]. Several short-term trials have compared polypills to placebo or no treatment, and in general have demonstrated effects on BP, cholesterol and side effects consistent with those expected from the component medicines [26,27]. The polypill-based strategy was rated as highly acceptable in these trials [4–6].

A recent systematic review and meta-analysis assessing the efficacy and tolerability of polypills vs. *placebo* in randomised controlled trials has demonstrated a reduction in SBP of 9.2 mmHg (95% CI: −13.4 to −5.0) and LDL cholesterol of 1.02 mmol/L (−1.37 to −0.67) [25]. Additionally, a recent Cochrane review by de Cates et al. [26] combining all available trials of polypills to date (*including placebo and active* comparator groups) demonstrated an overall reduction in SBP of 7.05 mmHg (95% CI: −10.18 to −3.87) and LDL cholesterol of 0.81 (95% CI: −1.09 to −0.53). This review noted that only 1 trial of the three comparing polypill use to usual care (UMPIRE — part of the SPACE Collaboration), measured adherence.

5. Conclusions

In conclusion, these results showed that polypill-based care in patients at high risk of CVD improved adherence and risk factor levels across a wide range of patient groups. There was little evidence of net benefit for those already well treated but there is likely to be a significant net benefit for those undertreated. Since most CVD patients globally do not take these medications at present, [28] this strategy could contribute significantly to the WHO goal of reducing CVD by 25% by 2025 [29].

Author contributions

AR conceived the idea for the Collaboration. All authors (except LB and SS) were founding members of the Collaboration. RW was the co-ordinator of the Collaboration, drafted all documents (co-drafted the statistical analysis plan with LB), co-ordinated the statistical analysis, data interpretation and drafted the manuscript. All authors (except LB and SS) were members of local trial steering committees and assisted with design of the statistical analysis plan, interpretation of data and

Table 4
Serious adverse events, overall and by system organ class.

Serious adverse event	Polypill n (%)	Usual care n (%)
Any cause	360 (23%)	316 (20%) p = 0.07
Renal and urinary disorders	106 (6.8%)	83 (5.3%)
Cardiac disorders	87 (5.5%)	74 (4.7%)
Infections and infestations	75 (4.8%)	62 (4.0%)
Gastrointestinal disorders	35 (2.2%)	31 (2.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	34 (2.2%)	31 (2.0%)
Nervous system disorders	32 (2.0%)	21 (1.3%)
Vascular disorders*	35 (2.2%)	17 (1.0%)
Injury, poisoning and procedural complications	29 (1.9%)	22 (1.4%)
Musculoskeletal and connective tissue disorders	26 (1.7%)	25 (1.6%)
Investigations	20 (1.3%)	17 (1.1%)
General disorders and administration site conditions	16 (1.0%)	16 (1.0%)
Respiratory, thoracic and mediastinal disorders	15 (1.0%)	14 (0.9%)
Metabolism and nutrition disorders	15 (1.0%)	9 (0.6%)
Reproductive system and breast disorders*	6 (0.4%)	17 (1.1%)
Hepatobiliary disorders	8 (0.5%)	4 (0.3%)
Eye disorders	7 (0.5%)	1 (0.1%)
Skin and subcutaneous tissue disorders	3 (0.2%)	4 (0.3%)
Surgical and medical procedures	4 (0.3%)	2 (0.1%)
Blood and lymphatic system disorders	5 (0.3%)	0 (0.0%)
Psychiatric disorders	1 (0.1%)	4 (0.3%)
Endocrine disorders	3 (0.2%)	1 (0.1%)
Immune system disorders	1 (0.1%)	1 (0.1%)
Congenital, familial and genetic disorders	0 (0.0%)	1 (0.1%)
Ear and labyrinth disorders	1 (0.1%)	0 (0.0%)
Social circumstances	0 (0.1%)	1 (0.1%)

* $p < 0.05$.

revision of the manuscript. LB and SS were responsible for the conduct of the statistical analyses, and revising of the manuscript. All researchers are independent from the funders. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. RW will act as guarantor for the study and confirms that the manuscript is an honest, accurate and transparent account of the analyses reported; no important aspects have been omitted and any discrepancies from the study as planned have been explained. RW, AR, AP, CB, VS and ST (SPACE Collaboration steering committee) had final responsibility for the decision to submit for publication.

Conflict of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request from the corresponding author) and declare that [1] all authors have support from Dr. Reddy's Laboratories for the submitted work; [2] no authors have relationships with other companies that might have an interest in the submitted work in the previous 3 years; [3] their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and [4] have no non-financial interests that may be relevant to the submitted work.

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References

[1] S. Yusuf, S. Islam, C.K. Chow, S. Rangarajan, G. Dagenais, R. Diaz, et al., Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE study): a prospective epidemiological survey, Lancet 378 (9798) (2011) 1231–1243.

[2] M. Lafeber, W. Spiering, K. Singh, R.K. Guggilla, V. Patel, R. Webster, The cardiovascular polypill in high-risk patients, Eur. J. Cardiovasc. Prev. Rehabil. (2011).

[3] World Health Organization, Secondary prevention of non-communicable disease in low and middle income countries through community-based and health service interventions(Geneva) 2002.

[4] A. Patel, A. Cass, D. Peiris, T. Usherwood, A. Brown, S. Jan, et al., A pragmatic randomized trial of a polypill-based strategy to improve use of indicated preventive treatments in people at high cardiovascular disease risk, Eur. J. Prev. Cardiol. (2014).

[5] V. Selak, C.R. Elley, C. Bullen, S. Crengle, A. Wadham, N. Rafter, et al., Effect of fixed dose combination treatment on adherence and risk factor control among patients at high risk of cardiovascular disease: randomised controlled trial in primary care, BMJ 348 (2014).

[6] S. Thom, N. Poulter, J. Field, A. Patel, D. Prabhakaran, A. Stanton, et al., Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial, JAMA 310 (9) (2013) 918–929.

[7] J.M. Castellano, G. Sanz, J.L. Penalvo, S. Bansilal, A. Fernandez-Ortiz, L. Alvarez, et al., A polypill strategy to improve adherence: results from FOCUS (Fixed-dose combination drug for secondary cardiovascular prevention) project, J. Am. Coll. Cardiol. (2014).

[8] R. Webster, A. Patel, L. Billot, A. Cass, C. Burch, B. Neal, et al., Prospective meta-analysis of trials comparing fixed dose combination based care with usual care in individuals at high cardiovascular risk: the SPACE collaboration, Int. J. Cardiol. 170 (1) (2013) 30–35.

[9] H.M. Liu, A. Patel, A. Brown, S. Eades, N. Hayman, S. Jan, et al., Rationale and design of the Kanyini guidelines adherence with the polypill (Kanyini-GAP) study: a randomised controlled trial of a polypill-based strategy amongst indigenous and non-indigenous people at high cardiovascular risk, BMC Public Health 10 (2010) 458.

[10] V. Selak, C.R. Elley, S. Crengle, M. Harwood, R. Doughty, B. Arroll, et al., Improving adherence using combination therapy (IMPACT): design and protocol of a randomised controlled trial in primary care, Contemp. Clin. Trials 32 (6) (2011) 909–915.

[11] S. Thom, J. Field, N. Poulter, A. Patel, D. Prabhakaran, A. Stanton, et al., Use of a multidrug pill in reducing cardiovascular events (UMPIRE): rationale and design of a randomised controlled trial of a cardiovascular preventive polypill-based strategy in India and Europe, Eur. J. Prev. Cardiol. (2012).

[12] New Zealand Guidelines Group, New Zealand Cardiovascular Guidelines Handbook: a Summary Resource for Primary Care Practitioners, New Zealand Guidelines Group, Wellington, 2005.

[13] World Health Organisation, Adherence to Long-term Therapies. Evidence for Action, WHO, Geneva, 2003.

[14] T.P.A. Debray, K.G.M. Moons, G.M.A. Abo-Zaid, H. Koffijberg, R.D. Riley, Individual participant data meta-analysis for a binary outcome: one-stage or two-stage? PLoS ONE 8 (4) (2013), e60650.

[15] C.P. Cannon, Can the polypill save the world from heart disease? Lancet 373 (9672) (2009) 1313–1314.

[16] M. Helfand, S. Carson, C. Kelley, Drug Class Review on HMG-CoA Reductase Inhibitors (Statins): Final Report, Oregon Health & Science University, Portland (OR), 2006.

[17] http://www.meddra.org/ (accessed 3rd September 2014).

[18] Pill Collaborative GroupA. Rodgers, A. Patel, O. Berwanger, M. Bots, R. Grimm, et al., An international randomised placebo-controlled trial of a four-component combination pill ("polypill") in people with raised cardiovascular risk, PLoS ONE 6 (5) (2011), e19857.

[19] R. Collins, R. Peto, S. MacMahon, P. Hebert, N.H. Fiebach, K.A. Eberlein, et al., Blood pressure, stroke, and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context[see comment] Lancet 335 (8693) (1990) 827–838.

[20] C. Baigent, A. Keech, P.M. Kearney, L. Blackwell, G. Buck, C. Pollicino, et al., Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, Lancet 366 (9493) (2005) 1267–1278.

[21] M.R. Law, J.K. Morris, N.J. Wald, Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies, BMJ 338 (2009), b1665.

[22] Antiplatelet Trialists' Collaboration, Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients, Br. Med. J. 308 (6921) (1994) 81–106.

[23] Cholesterol Treatment Trialists' (CTT) Collaboration, Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins, Lancet 366 (2005) 1267–1278.

[24] E. Soliman, S. Mendis, W. Dissanayake, N. Somasundaram, P. Gunaratne, I.K. Jayasingne, et al., A polypill for primary prevention of cardiovascular disease: a feasibility study of the World Health Organization, Trials 12 (1) (2011) 3.

[25] S. Yusuf, P. Pais, A. Sigamani, D. Xavier, R. Afzal, P. Gao, et al., Comparison of risk factor reduction and tolerability of a full-dose polypill (with potassium) versus low-dose polypill (polycap) in individuals at high risk of cardiovascular diseases: the second Indian polycap study (TIPS-2) investigators, Circ. Cardiovasc. Qual. Outcomes 5 (4) (2012) 463–471.

[26] C.R. Elley, A.K. Gupta, R. Webster, V. Selak, M. Jun, A. Patel, et al., The efficacy and tolerability of 'polypills': meta-analysis of randomised controlled trials, PLoS ONE 7 (12) (2012), e52145-e.
[27] A.N. de Cates, M.R. Farr, N. Wright, M.C. Jarvis, K. Rees, S. Ebrahim, et al., Fixed-dose combination therapy for the prevention of cardiovascular disease, Cochrane Database Syst. Rev. 4 (2014), CD009868.
[28] S. Yusuf, S. Islam, C.K. Chow, S. Rangarajan, G. Dagenais, R. Diaz, et al., Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE study): a prospective epidemiological survey, Lancet 378 (2011) 1231–1243.
[29] World Health Organisation, Global Action Plan for the Prevention and Control of Noncommunicable Diseases, World Health Organization, Geneva, 2013.