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Editor's Choice

A pilot double-blind randomised placebo-controlled trial of the effects of fixed-dose combination therapy ('polypill') on cardiovascular risk factors

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SUMMARY

Aim: Our objective was to investigate the effects and tolerability of fixed-dose combination therapy on blood pressure and LDL in adults without elevated blood pressure or lipid levels. **Methods:** This was a double-blind randomised placebo-controlled trial in residents of Kalaleh, Golestan, Iran. Following an 8-week placebo run-in period, 475 participants, aged 50 to 79 years, without cardiovascular disease, hypertension or hyperlipidaemia were randomised to fixed-dose combination therapy with aspirin 81 mg, enalapril 2.5 mg, atorvastatin 20 mg and hydrochlorothiazide 12.5 mg (polypill) or placebo for a period of 12 months. The primary outcomes were changes in LDL-cholesterol, systolic and diastolic blood pressure and adverse reactions. Analysis was by intention-to-treat basis. **Results:** At baseline, there were differences in systolic blood pressure (6 mmHg). Taking account of baseline differences, at 12 months, polypill was associated with statistically significant reductions in blood pressure (4.5/1.6 mmHg) and LDL-cholesterol (0.46 mmol/l). The study drug was well tolerated, but resulted in the modest reductions in blood pressure and lipid levels. **Conclusion:** The effects of the polypill on blood pressure and lipid levels were less than anticipated, raising questions about the reliability of the reported compliance. There is a case for a fully powered trial of a polypill for the prevention of cardiovascular disease.

What's known?
Drug treatments to lower lipid levels and drug treatments to lower blood pressure both reduce the incidence of cardiovascular disease. There is a good theoretical case for the use of fixed-dose combination therapy (polypill) to reduce the incidence of cardiovascular disease in middle-aged and older adults.

What's new?
In middle-aged and older adults in a developing country, fixed-dose combination (polypill) therapy is well tolerated and compliance is satisfactory. Fixed-dose combination (polypill) therapy results in the more modest reductions in lipid levels and blood pressure than anticipated. It is feasible to conduct a full-scale trial of prevention with fixed-dose combination (polypill) therapy in a developing country.

Introduction

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide and is presently leading cause of death and disability in low and middle-income countries including Iran (1–3). Treatment of CVD is expensive, with more than 98% of health care expenditure on CVD devoted to treatment rather than prevention, (1,3), and such costs are increasing as new therapies emerge (4). There is therefore a need for coherent strategies for CVD prevention in low- and middle-income countries.

It has been established that there is a continuous relationship between cardiovascular risk and both blood pressures and cholesterol levels (5–8). As lowering elevated cholesterol or blood pressure reduces cardiovascular risk, it is therefore plausible that lowering these risk factors from average levels would also reduce cardiovascular risk (9,10). There is evidence that aspirin is effective in primary prevention of cardiovascular disease in individuals at high risk (11). Incidence of cardiovascular disease increases with age, therefore it has been argued that fixed-dose combination therapy (dubbed the 'polypill') including antiplatelet agents, blood pressure-lowering and lipid-lowering drugs could reduce incidence of cardiovascular disease in middle-aged and older adults (12). The most novel aspect of this proposal has been to offer treatment to individuals whose risk factors are below usual treatment levels, but who are nevertheless at high risk of cardiovascular disease because of their age and gender. There are a number of issues to consider in choosing the exact formulation of a polypill, and a greater number of active components promises greater effectiveness, but poses greater technical problems in developing the polypill (13). As a result of this, a number of variations of the polypill are currently under

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development, including three, four or five active drugs (14–16).

As the first step in investigating the effectiveness of a polypill, it is necessary to establish whether combination therapy has the anticipated effects on blood pressure and cholesterol levels when taken by individuals with risk factors below usual treatment levels. It is also necessary to establish whether the medication is well tolerated and whether patients adhere to the medication. This kind of question is best addressed in a randomised controlled trial of relatively short duration.

It has been argued that a prevention strategy based on a four drug polypill (two antihypertensive, aspirin and a statin) may be cost-effective, in low and middle-income countries (17–19). Iran is a middle-income country where cardiovascular disease is a major cause of mortality (20). As part of a programme to evaluate a polypill in Iran, we report on a double-blind randomised placebo-controlled trial investigating the effects of a four drug polypill in a middle-aged and older Iranian population. The trial was located in Golestan province (North-Eastern Iran), where cardiovascular disease accounts for 47.5% of deaths in older adults and where obesity, hypertension and diabetes and metabolic syndrome are common (21–23).

The aim of the study was to investigate the effects and tolerability of a polypill consisting of hydrochlorothiazide 12.5 mg, aspirin 81 mg, enalapril 2.5 mg and atorvastatin 20 mg in middle-aged and elderly adults who conventionally deemed to be healthy with no cardiovascular risk factors except for the age > 50 and would not currently be considered eligible for antihypertensive treatment. This was a four component polypill, because it was judged that inclusion of a third antihypertensive drug or a higher dose of enalapril might result in hypotensive symptoms.

Materials and methods

This is a double-blind, placebo-controlled trial. All men aged 50 to 79 or women age 55 to 79, who were resident in Kalaleh, Golestan, North Iran, free from diagnosed cardiovascular disease at baseline and not already taking antihypertensive, statins or antiplatelet therapy were eligible for inclusion in the study. The study area is semi-rural with income levels around the national average and where the great majority of older persons are illiterate.

Every household in the area was provided with information describing the study, it was publicised on local radio and television and individuals were invited to attend initial assessment if they met the inclusion criteria. At initial assessment, informed consent was obtained for collection of baseline data. Medical history was determined and a wide range of data was collected on lifestyle including diet, physical activity and smoking status. Two-seated blood pressures, 1 min apart after 5 min rest, and standing blood pressure were estimated. Height and weight were measured and fasting blood samples were taken to assess complete blood count, CPK, ESR, CRP, lipid profile, glucose, glycosylated haemoglobin, creatinine and electrolytes, liver function tests and uric acid.

All subjects were interviewed and educated about a healthy lifestyle and regular exercise by the enrolling physician. They were given a well-designed pictorial pamphlet describing all aspects of a healthy lifestyle. Illiterate subjects were asked to have the pamphlet read to them by their children at home every week. Several programmes were arranged with the local Golestan television station to show and discuss healthy lifestyles.

All family physicians, internists and cardiologists in the study region were invited to attend a lecture by the principle investigator (RM) about the polypill trial and the study goal, possible adverse effects of the polypill and their management. This lecture answered questions raised by local physicians, and secured professional support for the study and collaboration with research team to reduce the burden of CVD.

Individuals with contraindications to a component of the polypill were excluded. Contraindications to aspirin included hypersensitivity, previous bleeding peptic ulceration or recent peptic ulceration (within 3 months). Contraindications to thiazide diuretics included gout or hyperuricaemia (> 8 μmol/l in men or > 6 μmol/l in women). Contraindications to statins included liver disease. Contraindications to further blood pressure lowering included symptomatic postural hypotension or systolic blood pressure less than 90 mmHg at baseline. Individuals were excluded if they were unable to give full consent or to comply with the protocol because of mental or physical incapacity. Individuals with elevated total cholesterol levels or other laboratory abnormalities on initial assessment were initially reviewed and managed by the trial internist and subsequently referred to their family physician for further management.

Following initial assessment, individuals who were eligible for inclusion and gave their informed consent were provided with 2 months supply of placebo tablets for the run-in phase of the study. After the run-in compliance was assessed by history and pill count, blood pressure and lipid levels were repeated. Participants who no longer met the inclusion criteria or whose compliance was poor (< 70% of pill intake) were excluded. Patients were provided with further

information on the study, and informed consent was obtained for randomisation.

Participants were randomised by block randomisation through a computer-generated list of numbers. They were then allocated the correspondingly numbered blister packs containing either the 'polypill' as a single tablet or an identical placebo. Both polypill and placebo were manufactured by Alborz Darou pharmaceutical company. Participants and researchers were blind to the allocation.

Participants were followed up at 1, 4, 8 and 12 months. At follow-up visits, participants were asked about hospital admissions, cardiovascular events and possible adverse events. Researchers inquired about compliance and undertook pill counts, measured seated and standing blood pressure and took blood samples for laboratory tests. The study medication was dispensed, and patients were given a further follow-up appointment.

Participants who reported possible adverse effects during follow up were assessed by the trial internist. If appropriate, the medication was temporarily withdrawn to determine whether adverse effects were because of treatment. The internist restarted the study medication and if symptoms retuned after rechallenge, the study medication was discontinued.

The primary outcomes were blood pressure and LDL-cholesterol. Secondary outcomes included total cholesterol, triglycerides, HDL-cholesterol and fasting glucose, major cardiovascular events and any adverse reactions to medication. Analysis was by intention-to-treat basis. Mean systolic and diastolic blood pressures, all lipid levels, triglyceride levels and fasting glucose levels were compared using analysis of covariance (ANCOVA) adjusting for baseline differences in the model. In addition to reported adverse effects, abnormal laboratory tests are reported as elevations of CPK above 500 IU/l, elevations of AST above 50 IU/l or ALT above 40 IU/l and elevations of serum uric acid above 0.8 mmol/l. All analysis was carried out using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

Statistical analysis

Assuming a pretreatment blood pressure of 130 mmHg (standard deviation 20 mmHg), it was determined that a sample size of 504 was needed to have a power of 0.8 to detect a reduction in systolic blood pressure of 5 mmHg at a significance level of 0.05.

The trial was registered with Controlled Clinical Trials (24). The IRB of the Digestive Disease Research Center of Shariati Hospital reviewed and approved the study protocol and the informed consent forms. Ethical approval was obtained from the National Ethics Committee by the Deputy of Research at the Ministry of Health and Medical Education of the Islamic Republic of Iran.

Results

Between July 2006 and January 2007, 1733 people attended the assessment clinic. Of those assessed, 872 were included in the run-in phase of the study: 50.5% of those assessed. The main reasons for exclusion were hypertension (434), diabetes mellitus (219), history of CVD (193), taking aspirin (148), hyperlipidaemia (114), psychiatric illness (64), opium addiction (61) history of GI bleeding (40) and stroke (28). Subjects could have more than one reason for exclusion. Most exclusions were because of subjects who were already on treatment or had indications for treatment and therefore could not be randomised to a placebo. During the run-in phase, 258 participants were excluded, following which a further 65 were excluded and 74 participants were not randomised. Reasons for exclusion are shown in Figure 1. The remaining 475 participants were randomised (Figure 1).

Baseline characteristics are shown in Table 1. At baseline, all characteristics of the two groups were similar except that there were significant differences in blood pressure between the intervention and control groups (5.5 mmHg systolic $p = 0.001$; 2.9 mmHg diastolic $p = 0.002$), and more women were allocated to the intervention group ($p = 0.041$). Three hundred and forty-eight patients (348/475 = 73.3%) completed 12 months of follow up. Follow up was more complete in the control group than the intervention group (78.2% vs. 68.5%; $p = 0.016$ by Chi squared test). Reasons for losses to follow up are described in Figure 1.

Mean systolic and diastolic blood pressures and mean lipid levels during follow up are shown in Table 2. With the last measure carried forward, by ANCOVA, adjusting for differences at baseline, systolic blood pressure was 4.5 mmHg ($p < 0.001$) and diastolic blood pressure 1.6 mmHg ($p < 0.032$) lower in the intervention than control group at the last follow-up visit. By the same method, LDL-cholesterol was 0.46 mmol/l (12.0%) lower ($p < 0.001$), and total cholesterol was 0.63 mmol/l (15.5%) lower ($p < 0.001$). Triglycerides were 0.16 mmol/l (11.3%) lower ($p = 0.005$), HDL-cholesterol was 0.01 mmol/l (0.9%) higher ($p = 0.575$) and fasting glucose was 0.17 mmol/l (3.3%) lower ($p = 0.008$) in the intervention than the control group.

Pill counts suggested that compliance was reasonable, with 89% of tablets taken in both intervention and control groups. One participant in the control group and none in the intervention group developed

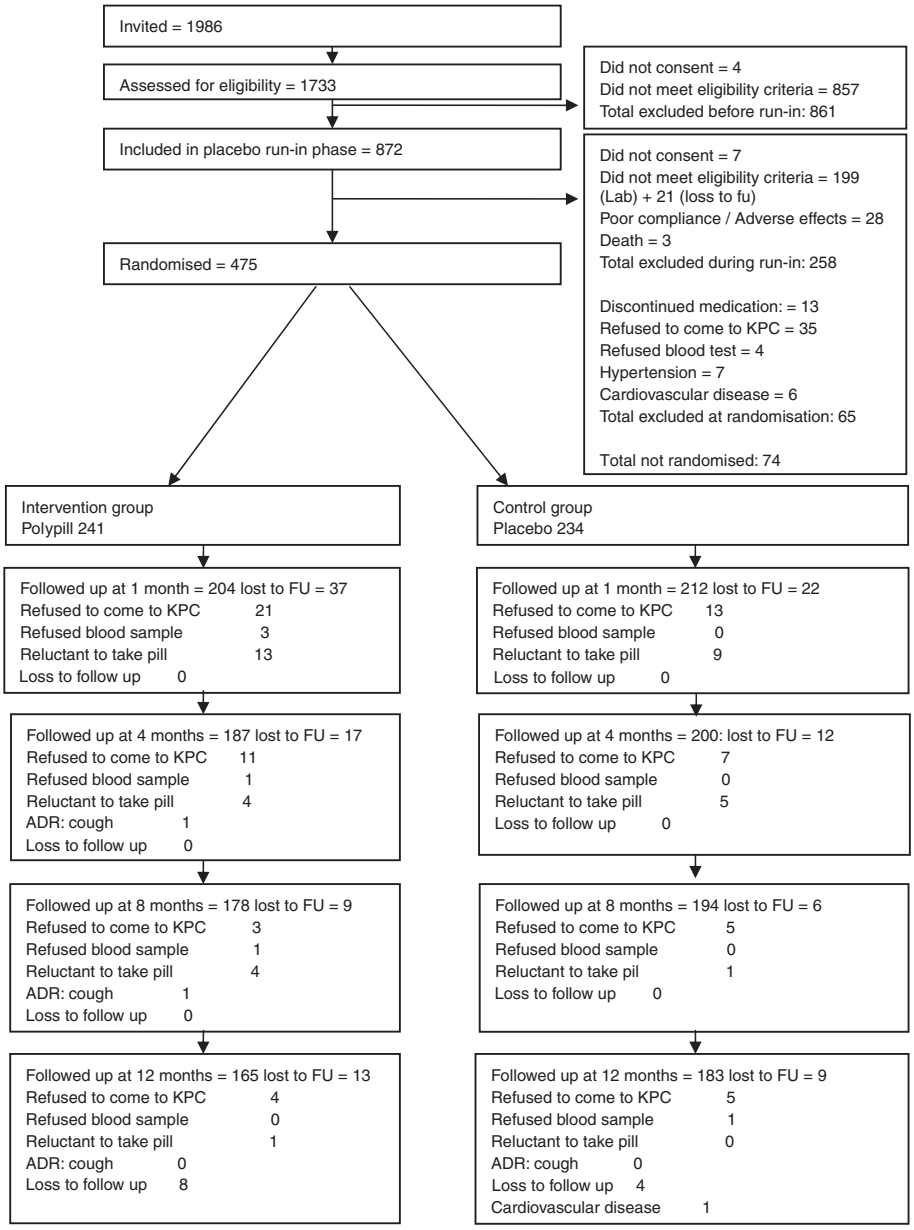

Figure 1 Recruitment and follow up

a non-fatal coronary attack. Two participants assigned to the intervention and none assigned to the control group discontinued the study medication because of cough (Fisher's exact test two sided p = 0.50). Six participants assigned to the control and none assigned to the intervention were started on additional drugs for hypertension (Fisher's exact test two sided p = 0.03). These subjects had average blood pressures of 150.2/89.2 mmHg at baseline. Other side effects were minor and did not result in the discontinuation of treatment.

Elevations of CPK above 500 IU/l were observed in nine intervention and two control participants (Fishers exact p = 0.063). No elevations higher than 700 IU/l were reported, and no participants reported clinical symptoms of myopathy. Abnormal liver function tests (elevations of AST above 50 IU/l or ALT above 40 IU/l) were observed in 43 intervention and 38 control participants (Fishers exact p = 0.714). No participants were found to have evidence of liver disease. Elevations of serum uric acid above 0.8 mmol/l were seen in 35 intervention and 31 control participants (Fishers exact p = 0.693).

Discussion

Our study is the first test of the effectiveness of a polypill in individuals without previous risk factors.

Table 1 Baseline characteristics of intervention and control groups

Parameters	Polypill	Placebo	p values
Number (total = 475)	(*n* = 241)	(*n* = 234)	
Age (years) ± SD	59.0 ± 6.5	59.1 ± 7.3	0.856
Gender (% female)	37.8	28.6	0.041
Systolic blood pressure (mmHg) ± SD	124.8 ± 17.3	130.3 ± 17.4	0.001
Diastolic blood pressure (mmHg) ± SD	78.4 ± 10.4	81.2 ± 9.7	0.002
Weight (kg) ± SD	68.7 ± 11.8	69.1 ± 12.1	0.729
Body mass index (kg/m^2) ± SD	26.4 ± 4.3	26.0 ± 4.2	0.316
Waist circumference (cm) ± SD	92.7 ± 12.0	91.6 ± 11.4	0.307
Total cholesterol (mmol/l) ± SD	5.26 ± 1.01	5.26 ± 1.00	0.987
LDL-cholesterol (mmol/l) ± SD	2.97 ± 0.68	3.02 ± 0.67	0.410
HDL-cholesterol (mmol/l) ± SD	1.14 ± 0.27	1.10 ± 0.25	0.063
Triglyceride (mmol/l) ± SD	1.42 (1.33–1.51)	1.48 (1.39–1.56)	0.382
Fasting glucose (mmol/l) ± SD	5.16 ± 0.73	5.16 ± 0.87	0.971
AST (IU/l) 95% CI	27.6 (24.6–31.0)	28.3 (25.1–31.8)	0.771
ALT (IU/l) 95% CI	18.4 (16.1–20.9)	19.3 (16.8–22.1)	0.610
CPK (95% CI)	92.3 (85.1–100.0)	95.9 (88.9–103.3)	0.491
Na+ (mmol/l) 95% CI	144 (143.4–144.5)	143.8 (142.4–145.2)	0.825
K+ (mmol/l) 95% CI	4.47 (4.43–4.52)	4.48 (4.44–4.52)	0.881
Creatinine (mg/dl) 95% CI	0.96 (0.95–0.98)	0.98 (0.96–1)	0.301
Smoking status (current, %)	19.1	23.5	0.263

*Values for categorical variables are proportions.

Table 2 Changes in primary and secondary outcomes adjusted for baseline differences

Measurement	Visit	Intervention (mean)	*N*	Control (mean)	*N*	GLM mean difference	p value
Systolic BP	Baseline	124.8	241	130.3	234	−4.5	< 0.001
	Final visit	121.1	241	129.0	234		
Diastolic BP*	Baseline	78.4	240	81.2	234	−1.6	0.032
	Final visit	77.6	240	81.2	234		
Total Cholesterol	Baseline	5.26	241	5.26	234	−0.63	< 0.001
	Final visit	4.37	241	4.99	234		
LDL-cholesterol	Baseline	2.97	241	3.02	234	−0.46	< 0.001
	Final visit	2.37	241	2.87	234		
HDL-cholesterol*	Baseline	1.14	240	1.10	234	0.01	0.575
	Final visit	1.24	240	1.21	234		
Triglycerides*	Baseline	1.42	240	1.48	234	−0.16	0.005
	Final visit	1.42	240	1.60	234		
Fasting glucose*	Baseline	5.16	240	5.16	234	−0.17	0.008
	Final visit	5.15	240	5.31	234		

*For each of these variables, one data item was missing from the database.

We found that fixed-dose combination treatment with aspirin 81 mg, hydrochlorothiazide 12.5 mg, atorvastatin 20 mg and enalapril 2.5 mg resulted in statistically significant, but unexpectedly the modest reductions in LDL-cholesterol and systolic blood pressure. A half standard dose of thiazide and quarter standard dose of ACE inhibitor would be expected to lower blood pressure by 12.0/6.0 mmHg in patients with a mean blood pressure of 154/97 mmHg and by 6.5/2.0 mmHg reduction in this population with a mean blood pressure of 125/78 mmHg (25). The observed effect was three quarters of this: 4.5/1.6 mmHg. Atorvastatin 20 mg would be expected to reduce LDL-cholesterol by

43% (9). The observed effect was a 15.5% reduction in LDL-cholesterol, about one-third of that predicted. The lower than expected effects on blood pressure and LDL-cholesterol are consistent with either poor compliance or with lack of drug efficacy. Our reductions in blood pressure and LDL are slightly smaller than those reported in a recently published study of a five component polypill in India: 7.6/5.6 mmHg for blood pressure and 0.70 mmol/l for LDL-cholesterol (26). However, the Indian study included three antihypertensive drugs and reported findings after 12 weeks of follow up, whereas we used two antihypertensive drugs and reported findings after 52 weeks.

Further detailed investigation of compliance with the study medication was conducted by interviewing 20 participants after the study had been completed. Participants indicated that they were happy to take the study medication daily despite realising that it may be an inactive placebo. Most participants admitted to occasionally forgetting to take tablets, sometimes failing to take medications with them when travelling and during harvesting time being unable to attend the study centre before their supply of tablets had been completed. Some of the subjects were not at home when we called them to give the reminder (15%). Overall, compliance was estimated to be about 65–70%. This level of compliance suggests that the drug may have been less efficacious than predicted. Further bioequivalence studies are planned to investigate this possibility. Furthermore, as we have longer follow up than the Indian trial (26), our estimated compliance may be closer to the true situation when the medication is offered to the general population in the long term.

Our study has some weaknesses. We observed differences in blood pressure and gender at baseline. This implies that there may have been deficiencies in the randomisation process which we have been unable to clarify. However, the analysis has attempted to deal with this by adjusting for differences at baseline. We also observed that although few adverse effects were reported, more patients discontinued the polypill than the placebo, particularly during the first month of follow up.

How effective is a polypill likely to be? Since the start of this study, there have been two further clinical trials on the effects of aspirin in primary prevention of CVD. We conducted a meta-analysis of the effects of aspirin in primary prevention, including the studies included in a previous meta-analysis and three subsequent clinical trials (11,27–34). Using a random effects model, relative risk of coronary heart disease (CHD) with aspirin is 0.82 (95% confidence interval 0.69 to 0.98), and relative risk of stroke (CVA) is 0.93 (95% confidence interval 0.84 to 1.04). With 35% efficacy (consistent with our findings of the effects of atorvastatin), we would expect a relative risks of 0.93 ($0.82^{0.35}$) for CHD and 0.97 ($0.93^{0.35}$) for CVA. A 12 mmHg reduction in systolic blood pressure is predicted to be associated with relative risks of 0.75 and 0.65 for CHD and CVA respectively (6,35). With a 4.5 mmHg reduction in systolic blood pressure, we would expect relative risks of 0.90 ($0.75^{(4.5\div12)}$) for CHD and 0.85 ($0.65^{(4.5\div12)}$) for CVA. A 1.81 mmol/l reduction in LDL-cholesterol would be associated with relative risks of 0.39 and 0.83 on CHD and CVA respectively (9,11,12,25). With a 0.46 mmol/l reduction in LDL-cholesterol, we would expect relative risks of 0.79 ($0.39^{(0.46\div1.81)}$) for CHD and 0.93 ($0.85^{(0.46\div1.81)}$) for CVA. The combined therapy therefore has a RR of 0.66 for CHD and 0.79 for CVA (9,11,25); (Table 3). Given that CHD accounts for about four-fifths of CVD events, this equates to a relative risk of CVD of 0.69 (3). Our findings are consistent with the more modest reduction in CVD risk than that proposed by the authors of the recent Indian study (26). Indications from this pilot study are therefore that a four component polypill has the potential to reduce the incidence of CVD by about one-third. This effect size may be sufficient to be cost-effective (17). However, larger effects have been observed with high-intensity statin treatment alone (36). Estimated effectiveness

Table 3 Predicted effects of a polypill on coronary heart disease (CHD) and CVA

	Typical effect of treatment			Effects of treatment with observed efficacy		
		Relative risk			Relative risk	
Intervention	Effect on risk factor	CHD	CVA	Effect on risk factor	CHD	CVA
Aspirin	Typical compliance	0.82	0.93	35% efficacy	0.93	0.97
LDL-cholesterol	1.81 mmol/l	0.39	0.83	0.46 mmol/l	0.79	0.95
SBP	12 mmHg	0.75	0.65	4.5 mmHg	0.90	0.85
Total		0.25	0.52		0.66	0.79

depends on assumptions about the likely effects of LDL lowering. Using the more modest effect sizes derived from another meta-analysis gives an overall relative risk of CVD of 0.79 (37). Recent meta-analysis has suggested that the risks and benefits of aspirin are finely balanced: exclusion of aspirin, as suggested, would give an overall relative risk of 0.83 (38). To ensure that all subjects might benefit from participation in this pilot study, the research ethics committee required that all study participants were offered advice on lifestyle modification. We therefore made considerable efforts to educate the study population about the importance of lifestyle modification in prevention of CVD and provided all participants with an illustrated pamphlet, conducted several radio and television programmes to emphasise healthy life style. We also used the network of community women volunteers to promote a healthy lifestyle in the Kalaleh district. This demonstrates that pharmacological prevention need not preclude lifestyle changes.

This pilot study illustrates the problems faced when trying to undertake primary prevention of CVD in a developing country such as Iran with high risk of CVD. These include obtaining informed consent in a population with low levels of literacy, ensuring compliance and maintaining adequate follow up. Overall, the clinical trial was conducted successfully. The polypill appears to have been well tolerated, compliance was reasonable and few significant adverse effects were reported. There remain, however, considerable challenges. Our findings raise questions about the bioequivalence of the polypill used in this trial, and further studies are needed to elucidate this. Increasing the dose of enalapril to 5 mg or 10 mg would help increase the effect on blood pressure, as higher doses of ACE inhibitors are not associated with higher incidence of adverse drug reactions (25). Compliance may also be improved. Healthy people may be reluctant to take a regular medication and we suggest that a future large scale trial may therefore include people with CVD risk factors detected during the prerandomisation clinical or laboratory evaluation, as these have a greater capacity to benefit from treatment and may be more likely to comply with treatment. A fully powered trial investigating the impact of the polypill on cardiovascular events and all cause mortality is needed. Our findings confirm the feasibility of such a trial.

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Ethical approval

The IRB of the Digestive Disease Research Center of Shariati Hospital reviewed and approved the study protocol and the informed consent forms. Ethical approval was obtained from the National Ethics Committee by the Deputy of Research at the Ministry of Health and Medical Education of the Islamic Republic of Iran.

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