# A Pilot Double-blind Randomised Placebo-controlled Trial of the Effects of Fixed-dose Combination Therapy ('polypill') on Cardiovascular Risk Factors

***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 undertaken in residents of Kalaleh, Golestan, Iran. Following an eight week placebo run-in period, 475 participants, aged 50 to 79 years, who had no cardiovascular disease, hypertension or hyperlipidemia 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 into account the baseline differences, at 12 months, the 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 reported compliance. There is a case for a fully powered trial of the polypill for prevention of cardiovascular disease.

***Source:*** Malekzadeh F, Marshall T, Pourshams A, Gharravi M, Aslani A, Nateghi M, et al. *Int J Clin Pract.* 2010; **64:** 1220 – 1227.

***Comment:*** Although age-specific death rates from cardiovascular diseases (CVD) have declined in western countries since 1975, they have increased in developing countries such as Iran. CVD, as the most common etiology of death and disability in Iran, is the cause of nearly half of the mortalities in middle-aged and elderly Iranians.[1,2] Thus primary and secondary prevention of CVD should be a priority for the health care system of middle-income countries such as Iran; but more than 98% of CVD-associated health system expenditure is devoted to treatment rather than prevention. Therefore, strategies for prevention of CVD are now the top priority in countries with limited health system budgets like Iran.

The majority of patients dying from coronary heart disease (CHD) have at least one risk factor for CVD.[3] Although some risk factors for CVD such as age, gender and family history are non-modifiable, most are modifiable. These modifiable risk factors are prevalent and poorly controlled in the Iranian population.[4] A primary strategy is the combination drug therapy for prevention of modifiable risk factors. Wald and Law simulated the effect of a combination therapy termed the "polypill" and have shown that the polypill reduced ischemic heart events and stroke by 88% and 80%, respectively, with maximum adverse effects in 8% to 15% of subjects.[5]

Previous studies have established the benefit of a polypill for secondary prevention of coronary heart disease in 91% of patients who experienced MI and in 77% of patients who experienced stroke.[6] The pilot study by Malekzadeh and colleagues from Iran[7] is the first attempt to study the effect of polypill for primary prevention of CVD in middle-aged and elderly people with no known cardiovascular risk factors except for age. The aim of this pilot trial was to investigate the feasibility of a large scale interventional trial with adequate power and duration in a predominantly rural population. Although the duration of this study was only one year, it has shown the feasibility of a large scale trial. In addition to reductions in blood pressure and serum cholesterol levels, which were less than expected; the compliance and rate of adherence, which was close to 70%, particularly amongst asymptomatic subjects was more than anticipated. It also has clearly shown that the use of a polypill for at least one year's duration is quite safe, with only few adverse effects in this population.

Wald and Law have estimated that the combination of three antihypertensive drugs, all at half standard doses, would reduce an average of about 11 mmHg of diastolic blood pressure and result in the reduction of the incidence of ischemic heart events and stroke by 46% and 63%, respectively.[4] However, in the randomised clinical trial (RCT) of Yusuf and colleagues,[7] the combination of half standard doses of thiazide (12.5 mg), atenolol (50 mg) and ramipril (5 mg) resulted in 7.4 and 5.6 mmHg reductions in systolic and diastolic blood pressures, respectively. Therefore, Wald and Law seem to have over-

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estimated the preventive effect of the polypill. In the pilot study by Malekzadeh and colleagues,[8] the half standard dose of thiazide (12.5 mg) and quarter standard dose of Enalapril (2.5 mg), an angiotensin converting enzyme inhibitor, resulted in only 4.5 and 1.6 mmHg reductions in systolic and diastolic blood pressures, respectively. Thus the blood pressure reduction in this pilot study was considerably smaller than those of the RCT of Yusuf and colleagues. As compliance was sufficient, therefore the lower than anticipated effects of the antihypertensive drugs were probably due to lack of drug efficacy. Thus, increasing the dose or number of antihypertensive drugs in the polypill would be needed in the main phase of the Golestan study in Iran. Thus, we propose to increase the dose of current drugs of thiazide and ACE inhibitor in the main phase instead of adding a new drug. The total cost of this polypill is less than three dollars per month and if proven to be effective and safe in the main phase study, it would be a very cost-effective strategy for primary and secondary prevention of CVD, particularly in low and middle-income countries.[9]

One of the main challenges for a polypill primary prevention trial is the aspirin component, which has been demonstrated by two recently published meta-analysis to cause a nearly one percent increase in absolute risk of major GI bleeding compared to placebo.[10] Published data available from six large-scale primary prevention trials and their meta-analyses have demonstrated that aspirin reduces the risk of first MI by about one-quarter to one-third, but the available data on stroke and cardiovascular death are inconclusive.[10] A cost-effective analysis has shown that benefits outweigh the risks only when the risk of a cardiovascular event in ten years exceeds 5 to 10 percent.[10] Regarding the high prevalence of CVD in aged Iranians,[11] using aspirin in the polypill could be beneficial in the primary prevention of CVD. Thus, we propose to use a polypill of four drugs in the main phase of the study: thiazide and an ACE inhibitor (at higher doses compared to the pilot study), a statin and aspirin.

The double blind, placebo-controlled randomized design used in the pilot study by Malekzadeh and colleagues[7] has resulted in strong internal validity, but limited external validity; thus results could not necessarily be extended to the general population.[12] The main phase of this study, which aims to find optimal guidelines for using the polypill in an actual rural population within the present healthcare infrastructure, need a more pragmatic design with a much higher external validity. Recently, the design of "cohort multiple randomized controlled trial" (cmRCT) has been introduced and consists of both pragmatic and explanatory randomized controlled trials. This design can offer combined appropriate internal and external validity and thus can be the preferred method for studies and trials whose results are supposed to be implemented in routine clinical practice.[12,13] This type of study design requires a large observational cohort of patients with the condition of interest in which the desired outcome is measured regularly and in which the capacity for superimposing multiple randomised controlled trials is present. Within such a cohort study, all eligible subjects to be enrolled to the desired interventional study are identified (NA). Then, some subjects of this group are selected randomly to receive the trial intervention (nA). At the end of the study, outcomes would be compared between the randomly selected patients (nA) and the eligible subjects randomly not selected who receive the usual care within the cohort (NA - nA). In this manner the intervention is compared with routine care, not with placebo.[12] The "Golestan Cohort Study" was launched in 2003 in Golestan Province on more than 50,000 subjects in which multiple variables including risk factors of CVD have been regularly assessed. Thus, instead of a double blind randomised trial used in the pilot study by Malekzadeh et al.,[8] we propose to use the cmRCT design within the Golestan Cohort Study.[2] Then, the main question of this study would be "Is it beneficial to suggest a polypill for all elderly individuals?" Besides, the absence of a placebo would probably increase long-term adherence of the subjects.

Previous interventional studies on the polypill, namely the study by Malekzadeh and colleagues[8] and the RCT of Yusuf and colleagues,[7] have assessed surrogate outcomes instead of primary outcomes of CVD. Risk factors such as blood pressure and lipid profile are usually used as surrogate outcomes because of short-term follow up in the pilot phase studies; while the main study outcomes should be MI and stroke.[14,15] In other words, the choice of specific therapy should be determined by evidence of what *does* work, and not on what *seems to* work or *ought to* work. Good surrogates that could be used when measuring primary outcomes are excessively invasive or unethical.[14,16] Therefore, in a polypill study, assessing primary outcomes of MI and stroke are necessary. Assessing effects of polypill on cardiovascular events needs a much longer follow-up period compared to assessing the effects of this drug on CVD risk factors. Thus, we propose to assess the primary outcomes (cardiovascular events and cardiovascular associated deaths) as well as surrogate outcomes (risk factors of CVD) in a follow-up period of at least five years during the main phase of the polypill study.

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