Commented Summary from Current Medical Literature

# "An International Randomized Placebo-Controlled Trial of a Four-Component Combination Pill ("Polypill") in People with Raised Cardiovascular Risk"

***Summary*:** There is widespread interest in the potential for combination cardiovascular medications consisting of aspirin and other agents to lower blood pressure and cholesterol (polypills) to reduce cardiovascular diseases (CVDs). However, no reliable placebo-controlled data are available on both efficacy and tolerability.

We conducted a randomized, double-blind placebo-controlled trial of a polypill (aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg and simvastatin 20 mg) in 378 individuals with no indications for any component of the polypill, whose estimated five-year CVD risks were over 7.5%. The primary outcomes were systolic blood pressure (SBP), LDL-cholesterol and tolerability (proportion discontinued randomized therapy) at 12 weeks follow-up.

At baseline, mean blood pressure was 134/81 mmHg and mean LDL-cholesterol was 3.7mmol/L. Over 12 weeks, polypill treatment reduced SBP by 9.9 (95% CI: 7.7 to 12.1) mmHg and LDL-cholesterol by 0.8 (95% CI: 0.6 to 0.9) mmol/L. The discontinuation rates in the polypill group compared to placebo were 23% vs. 18% (RR 1.33, 95% CI: 0.89 to 2.00, *P*=0.2).There was an excess of side effects known to the component medicines (58% vs. 42%, *P*=0.001), which was mostly apparent within a few weeks and usually did not warrant cessation of trial treatment.

This polypill achieved sizeable reductions in SBP and LDL-cholesterol but caused side effects in about 1 in 6 people. The halving in predicted cardiovascular risk is moderately lower than previous estimates, with a moderately higher rate of side effects. Nonetheless, substantial net benefits would be expected among patients at high risk for CVDs.

***Source***: PILL Collaborative Group, Rodgers A, Patel A, Berwanger O, Bots M, Grimm R, Grobbee DE, Jackson R, Neal B, Neaton J, Poulter N, Rafter N, Raju PK, Reddy S, Thom S, Vander Hoorn S, Webster R. PILL collaborative group, an international randomized placebo-controlled trial of a four-component combination pill ("polypill") in people with raised cardiovascular risk. *PLoS One*. 2011; **6(5):** e19857.

***Comment:*** Due to increased socio-economic status as well as the availability of vaccines and antibiotics, and improved hygiene in the 20th century in developed countries, an increase has been seen in life expectancy. Thus, chronic non-communicable diseases (NCDs) began to replace infectious diseases as the main causes of death. This epidemiologic transition started later in developing countries; consequently, in recent decades the burden of non-communicable diseases has risen disproportionately among populations of lower income countries.[1] Nearly 80% of deaths worldwide due to NCDs occur in low- and middle-income countries with about 30% of these occurring before the age of 60. Cardiovascular diseases (CVDs) are the leading cause of death among NCDs, accounting for nearly half of all NCD deaths.[2] While age-specific mortality rates for CVD began to decline in developed countries after 1975, they continue to rise in developing countries.[3,4] Projected figures suggest that coronary artery diesase (CAD) mortality rates will double from 1990 to 2020, and 82% of this increase will occur in the developing world. Iran is one of the most populated developing countries in the Middle East with a middle-income economy. CVDs are responsible for nearly half of the mortalities in middle-aged and elderly Iranians.[1,5] Cost-effective preventive measures are urgently needed to combat this ominous epidemic of CVD in developing countries such as Iran. Currently, less than 2% of Iran's health-care expenditure on CVD is allocated to preventive measures while treating CVDs imposes an enormous economic burden on the Iranian health-care system.[6]

The notion of a polypill was proposed in the beginning of this century as a promising cost-effective strategy that could potentially reduce cardiovascular diseases by more than 80%. This proposal was based on the following well-proven principles at that time[7–10]: i) the aim for a large change in reversible causal risk factors by using low-cost generic nonpatented medications in addition to life style modification; ii) concurrent modification of several reversible causal risk factors for maximal effect; iii) combining all medications in a single pill to decrease cost and increase compliance; and iv) administration of the drug to all individuals with an estimated risk of CVD events beyond a specified value, regardless of the levels of risk factors.

Individual components of the polypill have been proven effective for secondary prevention in large-scale long-term clinical trials with CVD primary outcomes as their endpoints. The demonstration of polypill's efficacy (as a combination of those components) in lowering surrogate markers of CVD in short-term trials provided sufficient corroborative evidence for its role in secondary prevention of CVD.[11,12] In the primary prevention of CVD, however, despite its theoretical merits and two short-term pilot studies that have shown a polypill containing low-dose aspirin, a statin and 2 to 3 antihypertensive medications to be safe and effective in lowering surrogate markers of CVD.[13,14] Large scale, long-term trials with hard outcome measures such as CVD-related mortality are still needed in different populations and health-care systems to provide sufficient evidence for the polypill's safety and efficacy. These data cannot be extrapolated from data available on secondary prevention. For instance, administering multiple agents in the form of a polypill to an individual who feels healthy could result in discontinuation of all the potentially beneficial agents if a minor side effect from one of the agents occurs. There are several concerns regarding motivation, ease of use, availability, side effect profiles, cost-effectiveness, and acceptability that need to be addressed for certain populations before population-based preventive strategies and guidelines can be formed around the polypill approach.

This randomized, placebo-controlled trial conducted by the program to improve life and longevity (PILL) collaborative group was planned to assess the efficacy and tolerability of a polypill as primary prevention. Participants were 378 individuals from seven

countries: Australia, Brazil, India, the Netherlands, New Zealand, the United Kingdom, and the United States. This study was planned as a pilot study for future large-scale long-term trials in an international multiethnic population. The study's participants were chosen from a population of adults with no indications for treatment by any of the components of a polypill based on current local guidelines. Participants, however, all had an estimated five-year CVD risk of at least 7.5% using the Framingham risk estimate. Soliman et al.[15] studied the polypill as primary prevention in individuals with an estimated ten-year total CVD risk score ≥20%, based on country-specific WHO CVD risk prediction charts. Yusuf et al. studied the effects and tolerability of a polycap (three blood pressure lowering agents, a statin, and aspirin) as primary prevention in individuals older than 45 with at least one conventional risk factor for CVD.[13] Malekzadeh et al. and Wald et al. studied the polypill as primary prevention using age above a specified value as the only eligibility criterion (55 and 50 years, respectively).[14,16] Although not universally agreed upon, it has been proposed that among people without CVD, age is the most important determinant of CVD risk and overall CVD risk assessment algorithms using multiple risk factors may add little to improve the results.[8,10,17]

The agents used as fixed dose combination therapy for primary prevention of CVD are more or less the same across different clinical trials. Different polypill formulations vary mainly in their side effect profiles and tolerability rather than their efficacy.[18] The inclusion of aspirin is still open to debate because of the increased risk of serious hemorrhage associated with its use. Aspirin's cost-effectiveness in individuals with an estimated ten-year risk of CVD events >6% – 10% and its possible added benefits in cancer prevention are the reasons for aspirin's inclusion in polypill formulations for primary prevention.[19] Also, the use of angiotensin receptor blockers (ARBs) instead of angiotensin converting enzyme inhibitors (ACEIs) in polypill combinations are well justified due to their increased tolerability.[18]

The blood pressure and LDL cholesterol reductions calculated by Wald and Law have not yet been achieved by these short-term pilot trials. In their original paper, Wald and Law estimated a 20/11 mmHg reduction in blood pressure and a 1.8 mmol/L reduction in LDL cholesterol from average pretreatment values of 150/90 mmHg and 4.8 mmol/L.[8] The study conducted by the PILL collaborative group reported a 9.9/5.3 mmHg reduction in blood pressure and 0.8 mmol/L reduction in serum LDL from average pretreatment values of 132/80 mmHg and 3.7 mmol/L, respectively. Yusuf et al. and Malekzadeh et al. have also reported lower reductions than the original estimates by Wald and Law even after non-adherence was taken into consideration.[13,14] A number of reasons might be responsible for this discrepancy: i) Law and Wald's estimates were based on meta-analyses performed in populations with higher pretreatment blood pressure and LDL levels in whom greater absolute reductions should be anticipated.[20,21] ii) Greater non-adherence and loss to follow up is encountered in trials when the polypill is given to healthy individuals with average blood pressure and LDL levels, in comparison with those on which the original meta-analyses were performed. Thus effects of a given dose of the medications are underestimated in polypill trials for primary prevention, even more so than in Law and Wald's estimations. iii) Yusuf et al. have shown that the effects of a polycap in reducing serum LDL is somewhat lower than simvastatin alone, the reasons for which are not yet fully understood.[13] iv) The blood pressure reduction achieved in the PolyIran study performed by Malekzadeh et al. was lower than similar studies, in part due to the lower dose of antihypertensive medications used.

Pilot clinical trials such as the one conducted by the PILL collaborative group are necessary for future large-scale trials to further elucidate the role of the polypill in primary prevention strategies for CVD. In a similar Iranian pilot study, Malekzadeh et al. have investigated the role of the polypill in primary prevention of CVD during 2006 – 2007 in residents of Kalaleh, Golestan, Iran. Based on the results of this pilot study, the main phase of the PolyIran study was launched in March 2011 to determine whether combination therapy of anti-hypertensive drugs, lipid lowering drugs, and aspirin (PolyIran tablet) is effective in preventing cardiovascular disease in Iranian people over the age of 50. With a target recruitment of 7000 participants and a follow up duration of five years, the PolyIran study is one of the largest clinical trials registered to date to explore the potential for a polypill to be incorporated into national guidelines for prevention of CVD.[22]

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