## Letters to the Editor

### Polypill: The Path from Concept to "Near" Reality in Preventing Cardiovascular Disease

***Dear Editor,***

In a landmark paper in 2003 Wald and Law coined the term "polypill", a pill containing antihypertensives, antiplatelet (aspirin), statin, and folic acid.[1] They estimated giving the polypill to those above the age of 55 years irrespective of cardiovascular risk would result in 88% reduction in ischaemic heart disease and 80% reduction in stroke.[1] Principle risk factors lowered by the polypill are blood pressure by anti-hypertensives (such as ACE Inhibitors and thiazide diuretics) and LDL cholesterol by using statins. The rationale relies on the fact there is no threshold below which reduction of such risk factors does not confer a beneficial effect. Although evidence for folic acid, which lowers the homocysteine levels, another marker of cardiovascular disease, has been refuted[2] all other components have proven track record to substantially reduce myocardial infarction and stroke. The polypill concept has important implication for middle and low income countries who will bear 80% of the global cardiovascular disease (CVD) related mortality by year 2020.[3] It is even truer in Iran where cardiovascular disease account for 47.5% of deaths. Limited resources in these countries have resulted in poor access to individual drugs that are part of the polypill for even secondary prevention. Therefore if proven of benefit polypill can have a major public health impact in the primary prevention of CVD. Recent trials reported in India[4] and other parts of the world[5,6] and a pilot study in Iran[7] have supported the concept, even though the effect size has been much less than the 80% mark reduction in CVD initially estimated by Wald and Law.[1] The Indian study estimated a reduction in cardiovascular heart disease by 62% and stroke by 48%.[4] A similar effect size was reported by the PILL Collaborative Group (PILL study) who estimated 50% reduction in CVD.[5] These findings have necessitated the call for revisiting the question on the accuracy of the size of effect the polypill can achieve, a question that Sepanlou and colleagues have examined in the previous issue[8] with an impressive accompanying editorial.[9]

First the researchers conducted an updated meta-analysis for each component of the polypill to estimate their effectiveness individually and in combination as a polypill. Then using the estimates they predicted the number of deaths that could be avoided in Iran each year. Their estimates suggest a combination of an ACE-inhibitor in half dose, a thiazide in half dose, aspirin and statin will reduce the ischaemic heart disease by half and stroke by 43%, resulting in approximately 40,000 fewer deaths each year. One of the key strengths of this paper is the sensitivity analysis conducted using different modelling approach (additive vs. multiplicative) in estimating the relative ratios of combined medication and the estimates derived for different combination of the components of the polypill. Their estimates are reasonably consistent with those found in the TIPS and PILL studies. The difference observed between studies can be partially explained by the combination of medications but more likely are a consequence of the difference in compliance in each study. For example the loss to follow-up was 27%, 16% and an impressive 1%, respectively in the Iranian, Indian, and multi-country (PILL study) studies. Non adherence to medication in the latter study among those followed up was 16% similar to the TIPS study.

However, still many key questions need to be answered before any implementation of the strategy at a population level is attempted. Critiques cite adverse events, medicalisation of primary prevention and cost of these drugs as key barriers in putting the concept into practice. Further evidence from large trials with cardiovascular disease and mortality end points are yet to be conducted. Aspirin for example can cause serious haemorrhagic side effects such as gastrointestinal bleeding and cerebral bleeding. Most agree aspirin should be avoided in primary prevention and only be part of secondary prevention strategy. Wald et al.[10] countering the argument of medicalisation of primary prevention states that it is the current screening process where individuals need blood pressure measurements, blood tests for cholesterol and being labelled as having hypertension or hypercholesterolaemia is what will result in medicalisation of an individual. The equitable approach of providing all those above the age of 55 years with a polypill will ensure 95% of those who go on to have heart attacks and stroke have the opportunity to be treated and will eliminate the need for traditional risk scoring systems like the Framingham prediction model that is complex and uses multiple risk factors to determine need for treatment.[10] Costs are unlikely an issue with these drugs being generic. Further recent surveys and studies have suggested acceptance among patients and physician for use of the polypill approach.[6,11]

The paper by Sepanlou et al.[8] acknowledges there are limitations and emphasise the need for monitoring adverse events, large scale population based studies with cardiovascular disease as end points and cost effectiveness analysis of the findings of such studies. Irrespective of the outcome on the effectiveness of the polypill saga, key interventions pivotal to prevention of CVD will be in implementing successful health policies. A good example is the introduction of antismoking legislations that can have greater impact in reduction of CVD outcomes. More work needs to focus on reduction in salt intake, trans-fat and saturated fat intake, sugar and alcohol across the global population. Similarly behavioural change will have an important role but they tend to be difficult to achieve, costly and are often not sustainable.[12] It is in this context polypill provides a simplistic alternative until substantial progress is made on these fronts.

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## Polypill for Primary Prevention: Has The Time Arrived?

***Authors' Reply***

Since the introduction of the concept of Polypill for cardiovascular disease (CVD) prevention, many studies have been conducted to determine whether it can be recommended as routine primary prevention of CVD. In the previous issue of the *Arch Iran Med* ( 2012; **15(9):** 531 – 537) we reported the estimated effectiveness of such a combination using updated meta-analyses of the component drugs.[1] Our estimates of the relative reduction in CVD mortality are more conservative than those previously reported,[2–5] because we estimated the effects of Polypill components on clinical endpoints rather than modeling their effects through reductions in blood pressure and serum cholesterol and we used a more conservative assumption for the combined effects of multiple treatments. None-the-less we may still have overestimated the achievable effects particularly, because adherence to treatment in the general practice settings is expected to be less than that reported in randomized trials.

Particular aspects of the cardiovascular disease epidemiology and health system characteristics in Iran may support large scale population-based administration of Polypill: CVD constitute 53% of deaths above age 30 in Iran[6]; 54% of these deaths are attributable to high blood pressure and 22% to high serum cholesterol.[7] The pills are produced locally at a low cost and an extensive primary health care network can enhance the feasibility and coverage of the policy.

However, we agree with Nirantharakumar and Marshal that before the use of Polypill can be recommended as a strategy for primary prevention of CVD on a national scale, its safety and acceptability should be evaluated in large scale randomized trials and its cost-effectiveness should be rigorously examined. It should also be noted that the coverage of the primary health care system in urban areas may need to be strengthened (possibly using family physicians) before such a national strategy can be successfully implemented. We also reiterate our emphasis that medical interventions should be combined and balanced with effective lifestyle interventions in a comprehensive national CVD prevention strategy.

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