

33 Polypill Co-Prescription for at the Risk Asian Indian in Chronic Non-Communicable Diseases

Abstract: Wald and Law's original 2003 BMJ paper on the Polypill, introduced the idea although it used data from single risk factor intervention. Cardiovascular disease and Stroke is on the rise in developing countries. Formulating low cost generic drugs in a single pill, and conducting studies locally, could lead to a solution - the Polypill. Such Polypill has now arrived. This Polypill tackles the risk factors that increase chances of cardiovascular events such as hypertension, LDL cholesterol, glucose platelet aggregation, and increased homocysteine levels in the blood. It may contain antihypertensives, aspirin, statins, and folic acid all at doses lower than the standard dose. This decreases side effects seen with standard doses of these drugs. The current polypills must have ramipril, atorvastatin, aspirin or clopidogrel. The Polypill would necessitate considerable patient education. The general population could use it as a substitute for efforts towards lifestyle modification. Patients using the pill in conjunction with exercise and diet programs can achieve phenomenal results. The Polypill approach is one of a public health intervention, rather than physician based treatment. This will lead to a significant cost advantage, and significantly more patients receiving such an intervention, especially in lower income groups. The Polypill is suitable for three groups of people: a) Those who have suffered a previous myocardial infarct or stroke. Patients with angina pectoris, diabetes mellitus, occlusive vascular disease and transient ischemic attacks must all consider the Polypill; b) All patients above the age of 55 years, since 96% of all cardiovascular events occur after this age; and c) Diabetics: Who are CV risk equivalent. Compliance in asymptomatic hypertensive patients who expect to see quick results that cannot be obtained with monotherapy, and the geriatric population, poorly compliant with multiple pills and dosing schedules, will improve with the Polypill.

The growing worldwide burden of cardiovascular and metabolic disease mandates the development and implementation of effective population-based preventive strategies. There has always been an element of truth in the old and slightly cynical description of popular geriatric polypills, the common collection of drugs for many elderly patients. Outside hospitals, in the effort to achieve reductions in premature or avoidable cardiovascular death and disability, many people are actually taking all or most of the components of the "Polypill," and we as doctors have reasonable grounds to believe in a mass benefit from doing so. In this era of evidence-based medicine meta-analysis is commonly more reliable than inspecting the results of a single trial, particularly if its power is low. Wald and Law have produced a classical paper in British Medical Journal in June 2003 which re-opened the 'Polypill' concept. In the Asian Indian perspective it is all the more relevant that independent of lifestyle we need preventive prophylactic pills which can save lives.¹

The incidence of cardiovascular disease (CVD) is rising at an alarming rate across the world. 15.3 million deaths have been reported due to CVD in 1996 and it is considered as a leading cause

of mortality amongst adults worldwide.² During the past 30 yrs, CVD rates have halved in US, Australia, Canada, France, Finland and Japan. However, they have more than doubled in India during the same period. It is estimated that CVD will be the leading cause of mortality and morbidity in the developing world by the year 2015.³

Western diet and lifestyle have increased the population levels of several of the causal risk factors and their combined effects have made CVD common. CVD can be avoided or delayed, but the necessary changes to Western diet and lifestyle are not practicable in the short term. Randomized trials have shown that drugs to lower the three most prevalent risk factors i.e. low density lipoprotein cholesterol,⁴ blood pressure⁵⁻⁹ and platelet function^{9,10} reduces the incidence of Ischemic heart disease (IHD) events and stroke.

There is now considerable evidence to show that Statins, Aspirin, Metformin and antihypertensive agents such as Thiazides and ACE inhibitors (or Angiotensin receptor blocker) can reduce morbidity and mortality due to cardiovascular disease. It could theoretically at least suggest that many patients with Type 2 diabetes would benefit from the SAMTA combination of therapies. Varadhan, et al have called this the SAMTA pill because, Indo-linguistically SAMTA means equality, and SAMTA pill may be a method of equalizing the increased cardiovascular morbidity and mortality in diabetes to that of the non diabetic population. The SAMTA pill offers the prospect of considerable reduction in cardiovascular morbidity and mortality in a primary prevention cohort of patients with Type 2 Diabetes. Our study confirms that the drugs were well tolerated with potential for increased prescribing of some or all of the components of the SAMTA pill. The radical Polypill concept stated that cardiovascular risk can be reduced by 88% through intensive polypharmacy addressing cardiovascular risk factors. This concept is based on a theoretical epidemiological model. Our study aimed to ascertain whether 50% reduction in coronary heart disease (CHD) in Steno-2 through multi-factorial pharmacological intervention could be modeled using the Polypill concept. The close correlation of actual Steno-2 and Polypill-predicted event rates may offer a 'Proof of Concept' for the Polypill. The Polypill or 'Aspostatinoprilololazide folate' may offer a realistic opportunity to reduce cardiovascular complications in patients with Type 2 diabetes.¹

The major limitation of the polypill, however, is that it embraces a common response of many in the medical community to modern chronic diseases, that is, the extrapolation of contemporary pharmacotherapies and modern technologies as a first-line strategy to stabilize overt cardiovascular disease. It also sends the wrong message to the population at large—that there is a “quick fix” for cardiovascular health in the form of a magic bullet. Because drug therapy and coronary revascularization have been largely unsuccessful in halting and reversing the epidemic, we argue that more emphasis must be placed on novel approaches to enhance current primary prevention guidelines, which require attacking conventional risk factors and their underlying environmental causes: high-fat and cholesterol diets, cigarette smoking, obesity, and physical inactivity. Recent studies challenge the widely held notion that CHD often (>50% of the time) occurs in the absence of any conventional risk factor, especially when more stringent cutoffs for abnormal blood pressure, cholesterol, and blood glucose levels are employed. Greenland et al reported that 87 to 100% of patients who experienced a fatal cardiovascular event had an antecedent exposure to at least 1 conventional risk factor (i.e., diabetes mellitus, cigarette smoking, hyperlipidemia, and hypertension). Similarly, Khot and associates found that >80% of patients with CHD had at least 1 of the 4 conventional risk factors and concluded that the resulting health risks are largely preventable by a healthy lifestyle.¹

Drug therapy, per se, also fails to address a major risk factor for cardiovascular disease—physical inactivity and/or low aerobic fitness. Epidemiologic data have established that physical inactivity increases the incidence of at least 17 unhealthy conditions, almost all of which are chronic diseases, resulting in approximately 250,000 premature deaths each year! One meta-analysis of 43 studies reported that the relative risk of CHD in relation to physical inactivity ranged from 1.5 to 2.4 (median value 1.9). Low aerobic fitness has also been shown to be an

independent and more powerful predictor of fatal cardiovascular events than other conventional risk factors. Although recent studies have identified multiple mechanisms by which regular physical activity may decrease morbidity and mortality rates associated with CHD perhaps Roberts summarized it best nearly 2 decades ago when he described exercise (running) as “... *an agent with lipid-lowering, antihypertensive, positive inotropic, negative chronotropic, vasodilating, diuretic, anorexigenic, weight-reducing, cathartic, hypoglycemic, tranquilizing, hypnotic and antidepressive qualities.*” In a randomized trial of 101 male patients with stable CHD and an angiographically documented stenosis amenable to percutaneous coronary angioplasty, compared with the latter, a 12-month exercise training program resulted in superior event-free survival and exercise capacity at lower costs. Contemporary guidelines suggest that patients should engage in >30 minutes of moderate-intensity physical activity such as brisk walking on most, and preferably all, days of the week. Nevertheless, randomized trials have now shown that a lifestyle approach to physical activity among previously sedentary persons is feasible and has similar effects on aerobic fitness, body composition, and coronary risk factors compared with a traditional structured exercise program. Fortunately, a low aerobic fitness level can be improved by regular endurance exercise, augmented lifestyle activity, or both, with each 1-MET increase in exercise capacity conferring an 8 to 12% reduction in mortality.¹

The effects of lifestyle change and drug therapy on cardiovascular risk reduction appear to be independent and additive. Intensive diet and exercise interventions can be highly effective in facilitating coronary risk reduction, complementing and enhancing medications, and in some instances, even outperforming drug therapy. However, the skyrocketing prevalence of obesity, diabetes mellitus, and physical inactivity suggest the need for “real world” interventions that are designed to circumvent and attenuate barriers to sustained lifestyle modification. These efforts go well beyond the physician’s office, and require major paradigm shifts that are supported by adequate patient education and encouragement, especially when individually tailored to the patient’s readiness to change, to serial monitoring and to extensive environmental change.¹

The impact of lifestyle on the risk of cardiovascular disease has been well established in clinical trials, but these results are often overlooked and underemphasized. In the Dietary Approaches to Stopping Hypertension (DASH) study, a diet that was rich in fruits and vegetables and low-fat dairy products but low in saturated fat significantly lowered systolic and diastolic pressure to the same extent as that observed in trials of drug monotherapy for mild hypertension. The higher the initial blood pressure reading, the greater the effect of the diet on lowering blood pressure. Moreover, it is estimated that a population-wide reduction in systolic or diastolic blood pressure of the magnitude observed with the combination diet would reduce the incidence of CHD and stroke by 15 and 27%, respectively. Accordingly, the DASH diet may represent an alternative to drug therapy for persons with hypertension, especially when combined with sodium levels of <100 mmol/day. More recently, the PREMIER clinical trial, which incorporated the DASH diet in 1 of 3 intervention groups, demonstrated the feasibility of comprehensive lifestyle modification in achieving substantial decreases in blood pressure, body weight, and sodium intake, and increases in physical fitness in patients with above-optimal blood pressure, including stage 1 hypertension.

Considerable data also strongly support the role of lifestyle intervention to improve glucose and insulin homeostasis. Tuomilehto, et al demonstrated the effect of changes in lifestyle on the development of Type 2 diabetes in high-risk overweight subjects with impaired glucose tolerance. A combination of a reduction in body weight (by >5%), a decrease in fat intake (to <30% of energy intake), a reduction in saturated fat intake (to <10% of energy intake), an increase in fiber intake (to at least 15 g/1,000 kcal), and an increase in exercise (to >30 minutes/day) resulted in a 58% reduction in the development of diabetes mellitus compared with results in the usual-care control group, although the average weight loss in response to the intervention was only modest (3.5 ± 5.5 kg by the end of year 2). Similarly, the Diabetes Prevention Program Research Group demonstrated that a lifestyle modification program with the goals of >7% weight

loss and >150 minutes of physical activity per week in overweight patients with impaired fasting glucose resulted in a 58% reduction in development of diabetes compared with placebo, whereas drug therapy with metformin reduced the risk by only 31%.¹

Several investigators examined the interaction between dietary changes, drug therapy, or both, on lipid and lipoprotein levels in patients with hypercholesterolemia. Their studies suggest that diets with 25 to 30% of calories from fat have only minimal effects on serum cholesterol and its subfractions when added to drug therapy, specifically statin treatment. The Lifestyle Heart Trial examined the effectiveness of a multifactorial, lifestyle modification program consisting of a low-fat vegetarian diet (>10% of calories as fat, polyunsaturated/saturated ratio >1, >5 mg cholesterol/day), exercise, smoking cessation, and stress management on the progression of coronary atherosclerosis. In the experimental group, total cholesterol decreased by 24% and LDL cholesterol by 37% versus 5% and 6% in the control group, respectively. High-density lipoprotein (HDL) cholesterol remained unchanged in both groups. It was suggested that concomitant exercise may have prevented the decrease in HDL cholesterol often associated with the reduction of serum lipids/lipoproteins by a low-fat diet. Moreover, Barnard et al reported that aggressive diet therapy (<10% calories from fat [<3% saturated]) combined with daily aerobic exercise results in additional substantial reductions in total cholesterol, LDL cholesterol, and triglycerides (19%, 20%, 29%, respectively) beyond those achieved with cholesterol-lowering drugs.¹

In a 4-week preliminary investigation, Jenkins, et al randomly assigned 55 healthy, hyperlipidemic adults to 1 of 3 interventions: a very low-saturated fat diet (control group), the same diet plus lovastatin (statin group), or a diet high in plant sterols, soy protein, viscous fibers, and almonds (dietary portfolio group), as recommended by the Adult Treatment Panel (ATP III) of the National Cholesterol Education Program. Of the 46 patients who completed the study, the control, statin, and dietary portfolio groups had mean decreases in LDL cholesterol of 8%, 31%, and 29%, respectively. Considering the expense, safety concerns, and intolerance related to statin use, an accompanying editorial suggested that patients who are motivated to adopt prudent diets might achieve meaningful first-line cholesterol reductions without pharmacotherapy.¹

Recently, Strangle, et al demonstrated that intense risk factor treatment combining a very low-fat diet (<10% calories as fat), weight control, regular exercise, and lipid active drugs dosed to target goals (LDL cholesterol <90 mg/dl, HDL cholesterol >45 mg/dl, triglycerides <100 mg/dl) further reduced cardiovascular events, deaths, revascularization procedures, and size and/or severity of stress-induced myocardial perfusion abnormalities compared with standard care cholesterol-lowering drugs alone. Because the trial was not randomized, it cannot unequivocally prove the potential independent benefit from lifestyle changes. Nevertheless, other studies have now shown that combining dietary therapy with drug treatment is more effective than drug treatment alone in improving brachial artery flow-mediated vasodilation, in correcting dyslipidemia, in reducing ambulatory blood pressure, and the risk of acute coronary syndromes.¹

The presumed expense of the polypill, when applied to everyone aged >55 years, would be staggering. If a fraction of these funds, instead, were used to greatly enhance effective nationwide primary prevention efforts (e.g., legislation to stop the proliferation of tobacco smoking, to increase physical activity in schools and in the community, and to foster the production and consumption of healthy foods), targeting patients of all ages, the results could have a profound effect on risk reduction for generations to come. Nonetheless, entrepreneurial interests, consumer demand, and the incremental benefits of combination drug therapies (i.e., aspirin, statins, beta blockers, and ACE inhibitors) may fuel the development of a cardioprotective polypill, which may come to fruition in the next few years. We recommend that treatment with the pill, or treatment with its respective components, individually or in combination, be accompanied by the following "User Directions": "Take medication each day in the prescribed dosage, followed or preceded by >30 minutes of moderate-to-vigorous physical activity, in combination with a low-fat, low-cholesterol diet, weight management, and the avoidance or cessation of cigarette smoking. Eat less, eat on time, walk more, smile and take a Polypill."¹

Heart attacks, stroke, diabetes and other preventable cardiometabolic diseases kill or seriously affect half the population of India. Modern Indian diet and lifestyle have increased the population levels of several of the causal “risk factors,” and their combined effects have made the diseases common. Cardiovascular disease or diabetes can be avoided or delayed, but the necessary changes to Modern Indian diet and lifestyle are not practicable in the short term. Randomized trials show that drugs to lower three risk factors—low density lipoprotein (LDL) cholesterol, blood pressure, and platelet function (with aspirin)—reduce the incidence of ischemic heart disease (IHD) events and stroke. Evidence that lowering serum homocysteine (with folic acid) reduces the risk of these diseases is largely observational but still compelling. Drug treatment to prevent IHD events and stroke has generally been limited to single risk factors, to targeting the minority of patients with values in the tail of the risk factor distribution, and to reducing the risk factors to “average” population values. This policy can achieve only modest reductions in disease. There is evidence from JNC VII on use of Thiazide diuretic and metformin with lifestyle in Diabetes Prevention Program that both the pills may have a role in the future. A large preventive effect would require intervention in everyone at increased risk irrespective of the risk factor levels; intervention on several reversible causal risk factors together; and reducing these risk factors by as much as possible.¹

Drug treatment is usually targeted at single risk factors and that too restricted to a small group of individuals who have high abnormal levels in order to bring them to average population levels. This approach will lead to modest reduction in risk of CVD in a population. As is known that the risk factors for CVD leads to atherothrombosis. Atherothrombosis reduces life expectancy by approximately 8-12 years¹⁰ (Table 1).

Unfavorable social and environmental conditions support unhealthy lifestyles often characterized by smoking; lack of regular physical activity; increasing consumption of fats, salt and carbohydrates; and inadequate consumption of fruits, vegetables and healthy oils. These factors along with genetic determinants challenge efforts in both primary and secondary prevention directed to CVD. However, although secondary therapeutic and behavioral preventive efforts for extant clinical illness will always be needed, more effort should be directed toward innovative and effective approaches for prevention.

Wald and Law described a strategy to prevent cardiovascular disease based on these three principles and quantify the overall preventive effect. They show that a daily treatment, the Polypill, comprising six components, each lowering one of the above four risk factors, would prevent more than 80% of IHD events and strokes, with a low risk of adverse effects. This strategy would be suitable for people with known cardiovascular disease and for everyone over a specified age (say 55), without requiring risk factors to be measured. In the June 28, 2003 issue of the British Medical Journal, an extensive literature survey based on various large meta-analyses of the efficacy and safety of the reduction of four cardiovascular risk factors (cholesterol, arterial blood pressure, platelet aggregation, homocysteine) leads to the conclusion that a combined pharmacological intervention should reduce ischemic heart disease events by 88% and strokes by 80% in at risk individuals. Recently, Wald and Law proposed a theoretical cardioprotective “polypill,” based on an analysis of the scientific literature (including >750 trials with 400,000 participants), as a population strategy to combat cardiovascular disease. The investigators boldly claimed that “it would be acceptably safe and, with widespread use, would have a greater impact on the prevention of disease in the Western world than any other single intervention.” The formulation was based on an analysis of the 6 components of the pill, which would include: a statin; 3 blood pressure-lowering drugs (e.g., a thiazide, a beta blocker, and an angiotensin-converting enzyme [ACE] inhibitor), each at half standard dose; folic acid (0.8 mg); and aspirin (75 mg). The strategy was to simultaneously reduce 3 cardiovascular risk factors (low-density lipoprotein [LDL] cholesterol, hypertension, and serum homocysteine), regardless of pretreatment levels combined with the antiplatelet effects of aspirin and the vascular protective effects of an ACE inhibitor and beta blocker.¹

They proposed in 2003 that a large preventive effect would require intervention in every one at increased risk irrespective of the risk factor levels, intervention on several reversible causal risk factor levels and reducing these risk factors by as much as possible.¹¹ Thus was introduced the concept of a polypill. They have proposed a polypill to target 4 potential risk factors; hypercholesterolemia, high blood pressure, increased platelet activation and hyperhomocysteinemia in all people more than 55 years of age and all patients of cardiovascular disease.¹² The composition of polypill suggested was a statin, low dose aspirin, three anti-hypertensives (Angiotensin Converting enzyme inhibitors, beta blockers and diuretics) and folic acid. Their results showed that a combination of drugs from different categories in low doses has greater efficacy and less adverse effects than one or two drugs given at standard doses. They also concluded that omitting a single component had minimal effects on the efficacy of the residual components, thus demonstrating the robustness of the polypill concept.¹² This strategy when given to all specified people and or patients without measuring the risk factors would reduce the risk of IHD and stroke by almost 80%.¹² It is proposed that on an average, people without known CAD will gain about 11-12 yrs of life free from a heart attack or stroke. The gain in life is substantial at all ages studied. The patients may also achieve their therapeutic goals faster than with monotherapy and this may be one of the reasons why compliance will increase. This applies especially to patients with asymptomatic conditions, such as hypertension and dyslipidemia, who may be tempted to discontinue their medication unless a measurable benefit is achieved within the first few months of treatment.¹³

The provocative analysis suggested that with a daily dose, the combination therapy would reduce coronary heart disease (CHD) events by 88% (95% confidence interval 84 to 91%) and stroke by 80% (95% confidence interval 71 to 87%). Other than the statin and blood pressure-lowering drugs, omitting a single ingredient had a relatively minor impact on the estimated reduction in CHD and stroke events, respectively. Depending on the precise formulation of blood pressure-lowering drugs, the proposed intervention would cause symptoms in 8 to 15% of persons taking the pill, warranting withdrawal in 1 to 2 of 100 and causing fatal side effects in < 1 in 10,000 users. If this calculation is correct, the benefits would substantially outweigh the risk in persons with documented cardiovascular disease and many others at increased risk. However, proponents acknowledged that components of the pill may be unsuitable for persons with some medical conditions (i.e., asthma) or those intolerant of aspirin.¹

Therefore, a new paradigm is proposed for the prevention of cardiovascular diseases.² This new strategy would consist in the systematic prescription to people with a history of heart attack or stroke, those with any form of obliterative atherosclerotic vascular disease or diabetes, and everyone aged 55 and older of a fixed combination of 6 pharmacological agents independently of initial risk factor profile. Such pharmacological formulation, called "polypill", should contain a statin, three blood pressure lowering drugs (each at half standard dose), aspirin (75 mg/day) and folic acid (0.8 mg/day). We discuss the pros and cons of this new paradigm. However, the efficacy of such "polypill" remains to be demonstrated in a large controlled clinical trial as well as its superiority as compared to a classical approach of cardiovascular prevention based upon the individual optimal correction of each risk factor thanks a dose titration of each pharmacological compound.¹

Polypill Formulation for India: Micro Pills, Macro Pills, Mega Pills

Polypills can be classified as micro pills (two or three components), macro pills (four or five components) and mega pills (more than six or seven components). Several 'micro' polypills are available in the Global and Indian Market. Two combination pills combining antiplatelet (Aspirin/Clopidogrel) and statins are very common as well as antihypertensive combination packs. Three combination micro polypills like aspirin, atorvastatin and ramipril is also available.

Macro polypill and mega polypill are under drug formulation program. The pharmaceutical technologies used are matrix based, polymer based or complex 'NILOP' technologies. These technologies have all the combination stability in-vivo and in-vitro as well as look at pill size and tolerability.

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Multiple Choice Questions

- 1. Omitting a single component of the polypill will lead to:**
 - A. Decrease in efficacy of the other components of the polypill
 - B. Increased efficacy of other components of the polypill
 - C. Increased side effects due to the other components of the polypill
 - D. Minimal effects on efficacy demonstrating the robustness of the polypill concept
- 2. The polypill should be indicated in the following individuals:**
 - A. Blanket primary prevention in groups with high rate of disease or those with one risk factor
 - B. Those requiring secondary prevention
 - C. Both a and b
 - D. All individuals >55 without any risk factors for CVD
- 3. Possible challenges with the polypill could be:**
 - A. It may lead people to think that such a pill would be a quick fix for an unhealthy lifestyle.
 - B. Problems with formulation such as should the polypill contain aspirin
 - C. Need for different polypills to cover different patient profiles
 - D. All of the above
- 4. For secondary prevention of CVD in the high risk group of patients who have had a coronary intervention the preventive therapy should include:**
 - A. Ticlopidine B. Cilastazol
 - C. Nitrates D. Aspirin
- 5. People who would benefit the most from a preventive pill containing aspirin and metformin are:**
 - A. Individuals with no risk factors for cardiovascular disease and age <55
 - B. Individuals >40 with family history of premature cardiovascular disease
 - C. Individuals >55 with no risk factors for cardiovascular disease
 - D. All of the above
- 6. The component of the Polypill that should be included in Indians is:**
 - A. Vitamin B₁₂ and folic acid
 - B. Trace elements
 - C. Ramipiril
 - D. Alpha methyl dopa
- 7. The most prevalent risk factors for CVD that are targeted with the polypill are:**
 - A. Hypertension
 - B. Hypothyroidism
 - C. LDL cholesterol
 - D. Platelet function
 - E. A, C and D

1. D 2. C 3. D 4. D 5. B 6. C 7. E