e38 The Polypill

K. Srinath Reddy, Nitish Naik, Ambuj Roy

Cardiovascular diseases (CVDs) are leading contributors to the global burden of disease, accounting for nearly 30% of global deaths and nearly 20% of disability-adjusted life years (DALYs) lost. Identification of multiple risk factors as well as interventions that alter risk by modifying one or more of them provide opportunities for reducing the risk of CVD through actions that impact on populations or directly on individuals. Major goals of preventive cardiology and clinical medicine are to identify individuals at a high risk of future CVD events and to intervene in order to substantially reduce their risk.

The decision to modify a risk factor has traditionally depended on the measured level of the risk factor, the risk of future CVD associated with that level, and the potential benefit of reducing it to a lower level through interventions that are cost-effective and safe. Evidence from observational studies, especially from large and long-term cohorts, has defined the prevention norms by indicating a continuous relationship between risk factor levels and CVD risk. Evidence from clinical trials has set the thresholds at which interventions are considered beneficial. Over the past two decades, prevention norms and clinical norms have converged because of accumulating new knowledge. For example, in the seventh U.S. Joint National Committee report on hypertension, the definition of normal blood pressure was lowered to <120/80 mmHg from <130/85 mmHg in the sixth report. Similarly, the target goals of low-density lipoprotein (LDL) cholesterol have been lowered progressively in patients with established coronary artery disease (CAD). However, clinical outcome data are scarce in patients when multiple risk factors are simultaneously targeted or when borderline abnormal values are treated. Hence, much interest was generated when Wald and Law proposed a polypill to target multiple risk factors, regardless of their levels, as a potentially effective intervention to reduce the risk of CVD. This chapter reviews the possible benefits and shortcomings of the polypill.

CARDIOVASCULAR DISEASE—MULTIFACTORIAL CAUSATION

Major risk factors related to CVD include behavioral factors, such as smoking, unhealthy diet, physical inactivity, and biologic factors, such as high blood pressure, elevated blood lipids, and diabetes. According to the INTERHEART study, nine risk factors [smoking; higher-than-normal ratio of apolipoprotein (apo) B to apoA; a history of hypertension and diabetes; abdominal obesity; psychological factors; and lack of daily consumption of fruits and vegetables, regular alcohol intake, and regular physical activity] account for ~90% of CVD risk globally, cutting across all major ethnic populations. Interventions, directed toward lowering many of these risk factors, have been shown to lower the risk of subsequent CVD events. Drugs that act on critical steps in the pathogenesis of atherothrombotic events, either by reducing risk factors (e.g., statins) or preventing pathologic processes (e.g., aspirin), have been shown to reduce vascular events. Both lifestyle measures and pharmacotherapy have been demonstrated to prevent or delay the onset of CVD-related clinical events in persons with high levels of one or more risk factors (*primary prevention*). They have also been shown to reduce the risk of recurrent events and to extend survival in persons who have manifest CVD (*secondary prevention*). Optimal drug therapy for secondary prevention of CVD currently includes aspirin, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins. These drugs have been shown to significantly reduce overall coronary and overall CVD event rates in patients with manifest CAD (**Fig. e38-1**). Some of them have also been demonstrated to be effective in reducing the risk of recurrent cerebrovascular events in persons who have earlier experienced a stroke or transient ischemic attack.

Statins have now become a cornerstone of secondary prevention strategies. They have been shown to improve survival, lower the risk of recurrent myocardial infarction (MI), and reduce the need for revascularization in patients with acute and chronic CAD. These benefits accrue regardless of measured blood cholesterol levels in patients with CAD. There is, however, a threshold of benefit, with little apparent clinical benefit in patients who achieved a <30% reduction in LDL cholesterol levels. In several randomized trials, patients receiving high-dose statin therapy (such as atorvastatin, 80 mg) benefited from a greater reduction in combined endpoints of cardiovascular mortality, MI, stroke, and need for revascularization when compared to patients receiving moderate-dose therapy (such as atorvastatin, 10 mg, pravastatin, 40 mg, or simvastatin, 20 mg/d).

β-Adrenergic blockers have clearly been shown to significantly reduce mortality after MI. In a meta-analysis of 25 trials, beta blockers were shown to reduce relative risk for overall death by 23% and reinfarction by 26%. While these benefits persist for many years on continuing therapy, they disappear on discontinuing therapy. Despite these proven benefits, many patients do not receive the benefit of these drugs for secondary prevention. The EUROASPIRE and WHO-PREMISE studies have shown suboptimal prescribing practices for CVD risk reduction among physicians in Europe and the developing countries, respectively. In a U.S. national survey on prescription patterns after MI, it was observed that beta blockers were not prescribed to nearly two-thirds of eligible patients in some regions. It has been estimated that if all post-MI patients received beta blockers over 20 years, then adverse outcomes of nearly one-fifth could be prevented, with a decrease in sudden death by 32% and a decrease in recurrent MI and revascularization by 27%.

The benefits of ACE inhibitors in patients with acute MI with left ventricular systolic dysfunction, as well as in those with chronic systolic heart failure, are well proven. Benefits of this class of drugs in patients at high risk for cardiovascular events, even without left ventricular dysfunction, have also been demonstrated. The HOPE study, which included patients with CVD or diabetes and at least one cardiovascular risk factor but the absence of left ventricular dysfunction, demonstrated a 26% reduction in cardiovascular death rates and a 16% reduction in overall mortality with ramipril. These benefits were observed even in the presence of other known therapies to lower CVD related events such as aspirin, beta blockers, and lipid-lowering drugs.

In patients with acute MI, aspirin has been shown to effect a 23% risk reduction in vascular mortality and a 10–40% risk reduction in

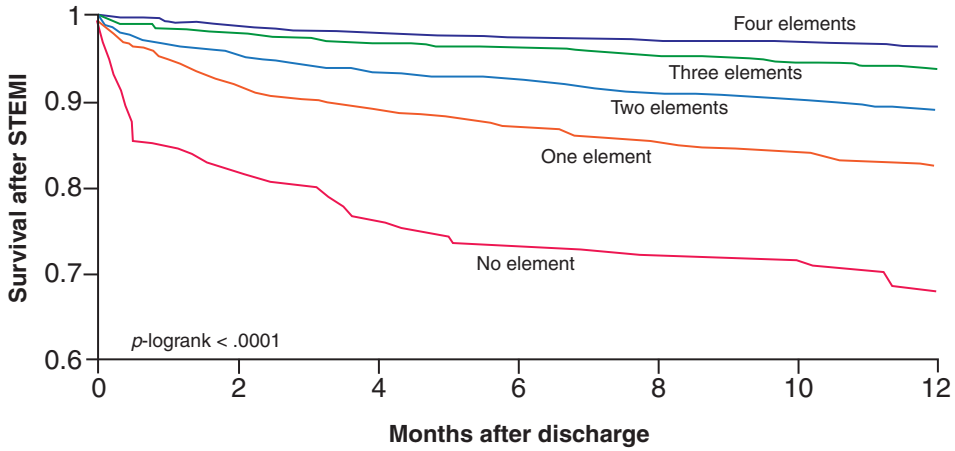

FIGURE e38-1 Post-MI survival in German hospitals is significantly improved in patients who receive four medications (aspirin, beta blocker, ACE inhibitor, and statin) when compared with those who receive zero, one, or two (*p*-logrank < .0001). *(Unpublished results from the MITRA registry. Reproduced from Sleight et al.)*

the composite endpoint of recurrent MI, stroke, or vascular death. However, it is also associated with an increased risk of gastrointestinal bleed and hemorrhagic stroke.

Lowering cardiovascular mortality by combinations of these drugs, when administered together, has been shown in some studies. In the ASCOT BPLA trial, calcium channel blockers and ACE inhibitors were observed to be more effective in controlling blood pressure than the traditional thiazide diuretics and beta blockers. Moreover, adding statins to the treatment led to a highly significant 36% reduction in the combined endpoint of nonfatal MI and fatal coronary heart disease. Analysis from the MITRA study demonstrated improved survival in post-MI patients who received these four medications (aspirin, beta blockers, ACE inhibitors, and statins) as opposed to those who received none to two drugs.

However, the protective role of combinations of these drugs for primary prevention of CVD has not been proved clearly. While statins and aspirin have been shown to reduce events in certain population subsets at high risk for CAD, actual data from clinical trials specifically designed to test the utility of this multidrug combination pharmacotherapy are lacking.

POLYPILL STUDY MODELS

Two studies have attempted to define the possible benefits of pharmacologic treatment of multiple risk factors in reducing cardiovascular events by modeling potentially achievable risk reduction with the use of multiple drugs. Wald and Law, in 2003, combined six drugs to model reduction of four cardiovascular risk factors—LDL cholesterol, blood pressure, serum homocysteine, and platelet function. The combined formulation included a statin (atorvastatin, 10 mg, or simvastatin, 40 mg), three blood pressure–lowering drugs (a thiazide diuretic, a beta blocker, and an ACE inhibitor, all at half the standard dose), folic acid (0.8 mg), and aspirin (75 mg). The authors suggested that the pill be used in all persons above the age of 55 years (as 96% of CVD events occur beyond this age in western populations) and in adult patients of any age with manifest CVD, regardless of their risk factors. In their model, the six drugs were used irrespective of the pretreatment risk factor levels, as the authors asserted that arbitrary thresholds of individual risk factors were poor predictors of future CVD events.

The concept of a continuum of risk was preferred to predefined cutoff levels that attempt to separate "normal" from "abnormal" levels. Published meta-analyses of multiple randomized trials were used to quantify the estimated benefit from this combination of drugs. The model factored a reduction of ischemic heart disease events at 2 years by 61% due to statins, by 46% due to anti-hypertensive drugs, by 16% due to folic acid, and by 32% due to aspirin. By multiplying the relative risk reduction from each class of drugs, the authors estimated that the combined effect of the four drugs would be an 88% reduction in ischemic heart disease events and an 80% reduction in stroke events (Table e38-1). Even if folic acid were omitted from the formulation, the authors estimate that 86% of ischemic heart disease events could still be averted. Similarly, absence of aspirin reduces the advantage of the polypill by only 5 percentage points to 83%. These benefits accrued with a low incidence of projected side effects. It was estimated that only 15% of patients would be expected to have adverse effects due to the formulation, mostly ascribable to aspirin. If all people >55 years used the pill, it was estimated that one in three people would benefit directly, gaining an additional 12–20 years of life-years without a coronary heart disease event or stroke.

Gaziano et al. further quantified these assertions in a subsequent study that examined cost-effectiveness of combination pharmacotherapy in reducing CVD in low-income and middle-income countries. Using a Markov model to assess cost-effectiveness, the authors used a combination of four drugs—aspirin, a calcium channel blocker, an ACE inhibitor, and a statin—for primary prevention. For secondary prevention, the authors substituted a beta blocker for the calcium channel blocker while retaining the other three constituents. For primary prevention, the authors included patients with a 10-year absolute risk of CVD of between 5% and 35%. This strategy thus required an additional hospital visit to assess CVD risk factors such as blood pressure, diabetes, serum cholesterol, and smoking status. The authors estimated that a nearly 50–60% reduction in CVD-related events could be expected if all patients with a 10-year absolute risk >5% were treated. This would lead to at least a 2-year increase in life expectancy in those above the age of 35 years. Using the secondary prevention strategy, the authors predicted a 10–15% reduction in lifetime risk of death due to CVD.

Using this model, the authors reported that the incremental cost-effectiveness of the primary prevention strategy was US$746–890 per quality-adjusted life year (QALY) for patients with a 10-year absolute CVD risk >25%, across six developing regions, as defined by the World Bank. The cost was higher in patients with lower levels of absolute 10-year cardiovascular risk, as more patients needed to be treated to achieve a similar reduction in CVD events, leading to higher expenditure and lower cost-effectiveness. However, incremental cost-effectiveness was still favorable for all primary prevention strategies, except for the strategy of treating all patients >55 years. For secondary prevention, incremental cost-effectiveness of the polypill was most favorable, at US$306–388 per QALY gained.

LIMITATIONS OF THE POLYPILL

Despite the perceived advantages associated with the delivery of multiple drugs in a single pill, including convenience of delivery, ensuring inclusion of all drugs considered essential for primary or secondary prevention, and possible improvements in compliance, several factors need to be accounted for before a polypill can actually be recommended.

The strongest objection to the concept of combination pharmacotherapy is the absence of any clinical trial to substantiate its merits. While several trials have documented the benefits of some of these classes of drugs administered separately in different patient subsets, such as post-MI survivors, those with CAD and left ventricular dysfunction, and other high-risk subsets, there is still paucity of data on the benefit of some of these drugs in certain patient subsets, e.g., ACE inhibitors in low-risk stable patients of CAD without left ventricular dysfunction. In the PEACE trial, which examined the efficacy of ACE inhibitors in lowering CVD events, no significant benefits were found with the use of trandolapril. Similarly, there is a lack of evidence to support the use of beta blockers in all patients with stable CAD. Aspirin also does not have a well-established role in preventing cardiovascular disease events in all women >55 years. Even the addition of a statin to aspirin does not significantly improve cost-effectiveness in primary prevention models, unless absolute risks are high.

TABLE e38-1 EFFECT OF POLYPILL ON RISK OF ISCHEMIC HEART DISEASE (IHD) AND STROKE, AS ESTIMATED BY WALD AND LAW, AFTER 2 YEARS OF TREATMENT AT THE AGE 55–64 YEARS

Risk Factor	Agent	Reduction in Risk Factor	% Reduction in Risk (95% CI)	
			IHD Event	Stroke
LDL cholesterol[a]	Statin[b]	1.8 mmol/L (70 mg/dL) reduction	61 (51–71)	17 (9–25)
Blood pressure	Three classes of drugs at half standard dose	11 mmHg diastolic	46 (39–53)	63 (55–70)
Serum homocysteine	Folic acid (0.8 mg/d)	3 μmol/L	16 (11–20)	24 (15–33)
Platelet function	Aspirin (75 mg/d)	Not quantified	32 (23–40)	16 (7–25)
Combined effect	All		88 (84–91)	80 (71–87)

[a]LDL, Low-density lipoprotein.
[b]Atorvastatin, 10 mg/d, or simvastatin or lovastatin, 40 mg/d taken in the evening or 80 mg/d taken in the morning.
Source: Adapted from Wald and Law.

The projected benefits of these combinations of drugs have been assumed using mathematical multiplication of relative risks. For some drugs, the authors have included the best-case scenario figures for risk reduction. For example, Wald and Law assumed a relative risk reduction of 61% of CVD events with the use of statins. However, data from many large randomized trials of statins have estimated the relative risk reduction to be at a more conservative level of 35%. These assumptions therefore need to be verified by an actual clinical trial. This is especially important in the case of primary prevention.

In secondary prevention trials, the sequential evaluation of cardioprotective drugs has seen each new drug being tested for incremental benefit when added to previously tested drugs and only then becoming standard therapy. Thus the value of combination therapy of multiple drugs (given separately and not as a single pill) is well proven. However, multiple drugs have not been used in such an incremental manner in primary prevention trials. It is essential that trial evidence, using major event-related endpoints, be generated for such multidrug combinations when used for primary prevention. In the case of secondary prevention, evidence on bioavailability, pharmacokinetics, and intermediate variables (risk factor levels) may suffice. Even in secondary prevention, some questions remain: Are beta blockers useful for secondary prevention of stroke? Are diuretics needed for secondary prevention of CAD?

The actual incidence of adverse events or other side effects associated with the use of the polypill is also unknown. Beta blockers, ACE inhibitors, calcium channel blockers, statins, and aspirin are all known to produce side effects requiring discontinuation of therapy. Although Wald and Law estimated that 15% of patients would be expected to discontinue therapy due to side effects, the actual incidence may be higher. Polypills would need to be available in different formulations to avoid anticipated side effects due to one or more components in susceptible persons. The dilemma of primary prevention becomes more obvious when an attempt is made to treat all patients alike, regardless of their absolute risk with one fixed combination of drugs. On the one hand, many asymptomatic persons with low absolute risk of events would be treated with little or no expected benefit; however, they would be exposed to the adverse effects of combination multidrug therapy. On the other hand, there would be high-risk patients who would be undertreated and might not reach the desired therapeutic goals. Without appropriate risk profiling, the latter patients would be diligently taking drugs but not accruing the maximum benefits. Although the population risk would still be lowered by such an approach, the individual at risk would not derive optimum benefit in spite of drug therapy.

Whether the polypill will necessarily improve compliance is not known. Although a low daily pill count does improve compliance, it is also affected by many other social and behavioral factors that are not necessarily overcome with the convenience associated with a polypill. Patient motivation and counselling, educational status, health education campaigns, and economic considerations are among the many factors that impact adherence positively and are unaffected by combination pharmacotherapy. Patients with overt clinical heart disease are more receptive to information regarding personal health behavior and its modification and are also more compliant with drug therapy. Long-term adherence to advice about behavior and drugs is lower when it is used for primary prevention in "real-world" settings. This can have a significant negative impact on the projected benefits.

An important assumption made by Wald and Law in targeting multiple risk factors simultaneously is that there are no clear demarcations between "normal" and "abnormal" levels of risk factors. They proposed, after appraising data from many observational and randomized trials, that there is a continuum of risk, with no specific risk factor thresholds that need to be targeted. It was recommended that interventions to modify risk factors should be guided by a person's level of absolute cardiovascular risk rather than the level of individual risk factors. Thus, patients with what is currently considered borderline elevation of multiple risk factors would derive benefit from interventions designed to modify those risk factors. However, data from the Framingham study suggest that 90% of CVD events occur in individuals with at least one preexisting major cardiovascular risk factor. Clustering of these risk factors is frequently observed in individuals and contributes to high level of absolute risk of CVD. Therefore, it is important to screen the population for these risk factors and then treat individuals at a high absolute risk with the combination pharmacotherapy, rather than treat the entire population >55 years with a blanket therapy. The ideal approach would be to assess an individual's global (absolute) cardiovascular risk, based on available algorithms for different populations, to maximize the benefits of the polypill and thus make it cost-effective, as shown in the study by Gaziano.

Another concern with use of a widespread pharmacologic intervention at the population level is the likely sense of complacency among both users and health care providers. Critics have expressed a fear that emphasis on healthy diet, physical activity, smoking cessation, and other lifestyle changes, which are essential elements in the management of these chronic diseases, may not be treated with the seriousness that they deserve. The polypill will not reduce the number of individuals acquiring a high-risk status in any population—it can only avert their future risk, if detected and treated. On the other hand, population-wide changes in diet, physical activity, and tobacco use are likely to reduce the number of individuals who enter this high-risk zone. Many other factors such as physician attitudes, cost-effectiveness, and long-term affordability have to be addressed before the promise of the polypill can be realized. These concerns would be best addressed by clinical trials that examine the benefits in the setting of both primary and secondary prevention.

IMPACT ON DEVELOPING COUNTRIES

CAD is an emerging epidemic in low- and middle-income countries. By 2020, >80% of all CVD-related deaths worldwide are expected to occur in the developing world. Moreover, even as age-adjusted cardiovascular disease rates are declining in the developed world, rates of CVD are rising rapidly in these low- and middle-income countries. The same risk factors responsible for CAD in the western population are operative in these countries, as shown by the INTERHEART study.

In the absence of well-resourced CVD prevention programs and limited public awareness of risk factors, the polypill appears attractive for such populations, especially for secondary prevention and high-risk primary preventions. It overcomes the problems of inadvertent drug omission by under-informed physician and provides the opportunity to include generic drugs such as lovastatin or simvastatin, enalapril, and propranolol to lower the cost of pharmacotherapy. The presence of a strong pharmaceutical industry in countries such as India offers the opportunity to lower the costs of drug production significantly, making the therapy more affordable and applicable. A World Health Organization report on chronic diseases suggests that a polypill could be made available for a little over US$1 per patient per month, using these generic products. Moreover, with the expected low side-effect profile of these pills, it may be possible to shift identification and treatment of high-risk individuals to non-physician health workers in these resource-poor countries, thereby lowering the cost and widening the access for effective risk reduction. However, the developing countries would need to place even greater emphasis on policies and educational interventions that protect their populations from the risk of CVD, while judiciously applying interventions such as the polypill.

CONCLUSIONS

The concept of a polypill to reduce the burden of CVD is attractive and seems to have great potential, especially in secondary and high-risk primary prevention. However, its role is presently speculative and needs to be assessed in randomized trials. It should not distract clinicians from the importance of managing risk factor levels; rather, it should enable persons at high risk of CVD to access affordable and easy-to-consume therapy for reducing that risk. It is also important that the polypill should not lull the patient and the physician into a false sense of security—continued emphasis on targeting modifiable risk behaviors such as smoking, sedentary lifestyle, and unhealthy diet

would continue to yield equal dividends. They would also be applicable to the wider population, with greater safety.

FURTHER READINGS

COMBINATION PHARMACOTHERAPY AND PUBLIC HEALTH RESEARCH WORKING GROUP: Combination pharmacotherapy for cardiovascular disease. Ann Intern Med 143:593, 2005

CONSTANTINO G et al: Prevention of cardiovascular disease with a polypill. Lancet 369:185, 2007

GAZIANO TA et al: Cardiovascular disease prevention with a multidrug regimen in the developing world: A cost-effectiveness analysis. Lancet 368:679, 2006

REDDY KS: The preventive polypill—much promise, insufficient evidence. N Engl J Med 356:212, 2007

SLEIGHT P et al: Benefits, challenges, and registerability of the polypill. Eur Heart J 27:1651, 2006

VASAN RS et al: Relative importance of borderline and elevated levels of coronary heart disease risk factors. Ann Intern Med 142:393, 2005

WALD NJ, LAW MR: A strategy to reduce cardiovascular disease by more than 80%. BMJ 326:1419, 2003

YUSUF S et al, on behalf of the INTERHEART Study Investigators: Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. Lancet 364:937, 2004