The Preventive Polypill — Much Promise, Insufficient Evidence

Summary: The rapidly increasing global burdens of cardiovascular disease and diabetes call for interventions that have a population-wide effect, as well as interventions that identify and protect individual patients who have a high risk of major adverse events. Such actions are especially needed in low-income and middle-income countries, which can ill afford the huge losses in human and financial resources that will result from unchecked development of clinical disease. Many drugs have been found to be highly effective in the primary or secondary prevention of cardiovascular diseases. These include aspirin, angiotensin-converting enzyme (ACE) inhibitors, statins, beta-blockers, and calcium-channel blockers. Despite their potential for saving lives by effectively reducing cardiovascular risk, these drugs have not been used optimally even in developed countries. Poor adherence to multidrug regimens is a common barrier to effective therapy. In low-income and middle-income countries, the unaffordable cost of such regimens represents another obstacle. Recently, as a way of overcoming these barriers, some observers have been advocating the concept of a “polypill” — a single pill that would include a number of key drugs. Wald and Law have proposed that the combination pill consists of aspirin, an ACE inhibitor, a beta-blocker, a statin, a diuretic, and folic acid. Since there is no trial evidence to suggest a benefit from the addition of folic acid or a diuretic to a regimen for preventing coronary disease that already includes two blood-pressure-lowering drugs, others have suggested combinations of four to five drugs that may be customized separately for primary prevention of cardiovascular diseases, secondary prevention of coronary heart disease, and secondary prevention of stroke. Recent trial evidence has been cited in support of the recommendation that primary prevention regimens should include a calcium-channel blocker, whereas secondary prevention regimens must include a beta-blocker. Aspirin, an ACE inhibitor, and a statin would be incorporated into both types of regimens. The availability of most of these drugs in a generic form may help to reduce the cost of a polypill, especially in countries such as India, with its active generic drug industry. Moreover, modeled economic analyses suggest that such multidrug regimens would be quite cost-effective in reducing the burden of cardiovascular diseases even in low-income and middle-income countries. Since current treatment guidelines recommend multiple drugs for the secondary prevention of cardiovascular disease, a polypill would probably be easily accepted for that indication.

In the area of primary prevention, however, the value of such a pill would have to be clearly demonstrated, rather than simply assumed. The World Heart Federation recently announced that it would support the development and evaluation of a polypill consisting of aspirin, an ACE inhibitor, and a statin. Two Indian drug manufacturers have already developed four-drug combination pills (the fourth drug being a beta-blocker) and will soon begin clinical trials. Such trials will provide further information on the cost-effectiveness, safety, and adherence profile of a combination pill and should reveal whether the polypill is a miracle or a mirage. Without such evidence, advocacy for the polypill would be a mere leap of faith. An interview with Dr. Reddy can be heard at www.nejm.org. Dr. Reddy is the president of the Public Health Foundation of India and a professor of cardiology at the All India Institute of Medical Sciences, New Delhi, India.


Comment: We agree with Dr. Reddy¹ that there is a need for investigating the effects of polypill in a high-risk population without cardiovascular disease. An example of such work is under way.² Tehran University of Medical Sciences and the University of Birmingham, UK are collaborating to run a pilot double-blind, placebo-controlled, randomized clinical trial with a four-component polypill in Golestan Province, northern Iran.

The population under study are men aged >50 and women aged >55 years with normal blood pressure and cholesterol levels and free from cardiovascular diseases, though with a high risk of cardiovascular diseases because of their age. Data from an ongoing cohort study suggested that over half of deaths in this population are due to cardiovascular diseases. Our polypill is a combination of aspirin 75 mg, hydrochlorothiazide 12.5 mg, enalapril 2.5 mg, and atorvastatin 10 mg. It is manufactured by a local pharmaceutical company. We intend to follow 500 patients for one year. We will measure compliance,
changes in blood pressure and cholesterol levels, the incidence of adverse-effects, and effects on quality of life.

To date, 816 patients have completed the two-month run-in period and we have recently begun randomization. If successful, we will follow this pilot study with a clinical trial fully powered to determine effects on cardiovascular events. We think that our study is possibly the first clinical trial of a polypill on the primary prevention of cardiovascular disease.

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References