

The Preventive Polypill — Much Promise, Insufficient Evidence

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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.¹

Many drugs have been found to be highly effective in the primary or secondary prevention of cardiovascular disease. 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 consist of aspirin, an ACE inhibitor, a beta-blocker, a statin, a

diuretic, and folic acid.² 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 disease, 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.³ 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 disease even in low-income and middle-income countries.³ 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.

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1. Reddy KS. Cardiovascular disease in non-Western countries. *N Engl J Med* 2004;350:2438-40.

2. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419. [Erratum, *BMJ* 2003;327:586.]

3. Gaziano TA, Opie LH, Weinstein MC. Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. *Lancet* 2006;368:679-86.

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