

RADICAL VISION:

A cocktail of cardiovascular drugs // Recommended for everyone over 55 // No prescription necessary // No need for a doctor's oversight // The brainchild of overly ambitious would-be pioneers, or truly the world's next wonder drug?

The Polypill

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Richard Smith, editor of the prestigious *British Medical Journal*, opened his June 28, 2003, editorial with this teaser: “It’s perhaps more than 50 years since we published something as important as the cluster of papers from Nick Wald, Malcolm Law and others.” Intrigued readers pored over the papers, which described an approach that “would have a greater impact on the prevention of disease in the Western world than any other single intervention.”

The intervention turned out to be a cardiovascular drug with an unusual strategy of delivery: Wald and Law envisioned that everyone over age 55, the population segment accounting for 96% of all deaths from coronary artery disease and stroke, would take the pill every day for the rest of his or her life. If all complied, 88% of heart attacks and 80% of strokes would be prevented, said the authors, who also opined that physicians need not be involved.

Wald and Law called their drug the Polypill, a combination of several powerful cardiovascular medications—a statin, an ACE inhibitor, a beta-blocker and a thiazide—as well as aspirin. And if in 2003 the Polypill was just a theory, last September at the World Congress of Cardiology in

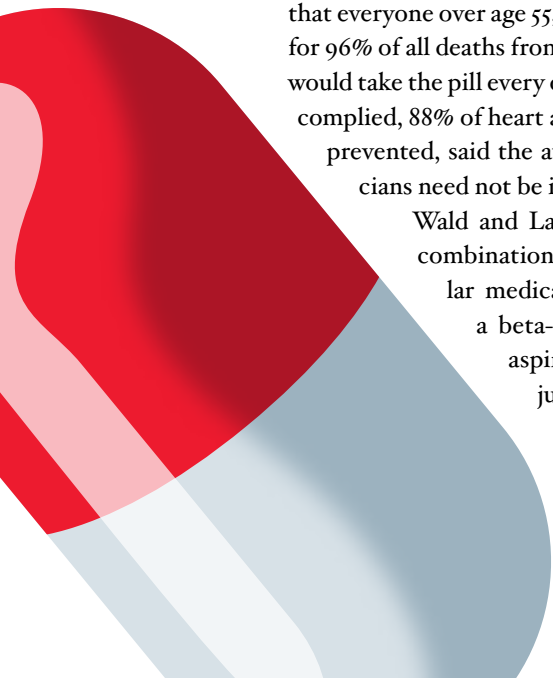


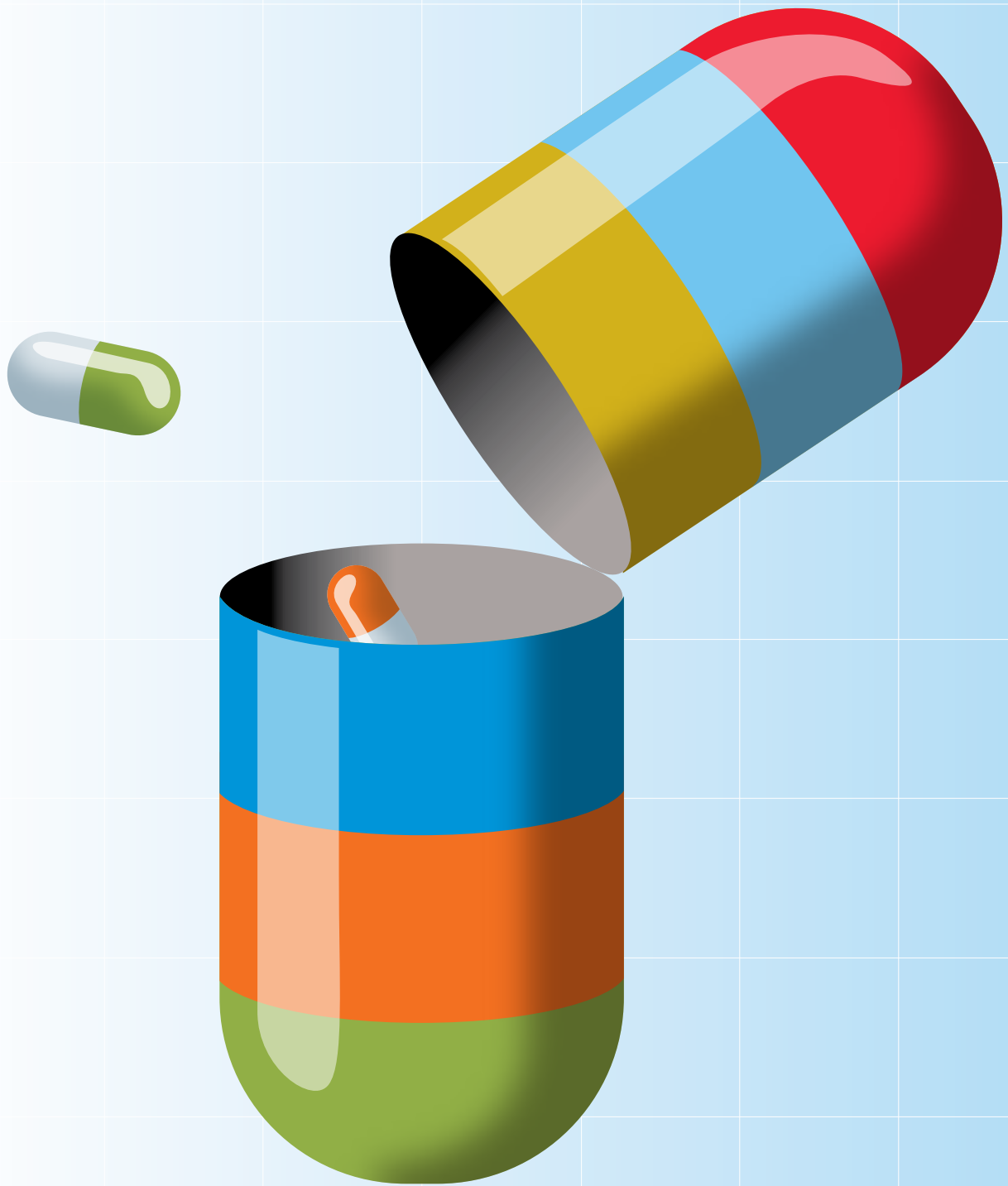
Barcelona, World Heart Federation president Valentin Fuster announced that a version of the pill could be introduced in Spain by 2009, while investigators in New Zealand and Australia are about to begin trials on alternate versions of the pill.

After the *BMJ* published the papers, physicians showered the journal with letters of concern—not only about whether the Polypill would work but also about whether it would even be desirable. “How nice...to live in a Polypill world,” wrote German scientists. “One for heart disease, one for mood, and maybe even one for finding the right partner.”

The Polypill idea is radical, in part because physicians generally prescribe powerful medications to healthy people only if they are at extremely high risk. But proponents contend that anyone living in the Western world today falls into the high-risk category and needs to reduce each of many cardiovascular-disease risk factors, not just the one or two surpassing some arbitrary threshold. Otherwise, those proponents warn, many of us could become part of the third of the population who die from an almost completely preventable disease.

Polypill fans or not, most physicians agree on one thing: Dying of a heart attack is not natural. “This is a disease we manufactured through the way we live,” says David Wald, a London cardiologist who is part of the Polypill team with his father, Nicholas, and Malcolm Law.





Cardiovascular disease is the No. 1 killer in the United States. In part, that prevalence stems from our lifestyles. We commute long distances to office jobs that allow no time for exercise and lead us to rely on processed or fast foods packed with salt, saturated and trans fats. As a result, our cholesterol and blood pressure readings are often too high to be healthy.

Nicholas Wald and Law propose addressing this problem with a new approach. What if we were to not focus exclusively on what has been a losing battle against our culture, and instead begin to address each of the many factors that contribute to heart disease before it becomes a problem? What if all risks—high blood pressure, cholesterol, homocysteine (an amino acid that has been linked to cardiovascular disease) and poor platelet function (clumped platelets can lead to a heart attack or stroke)—were reduced even in those whose test results put them in the normal range? “There’s no evidence of a threshold for these risk factors,” says David Wald. “There’s benefit in changing their level in everybody.”

Eventually, the Polypill team members want their pill to be available over the counter, like a multivitamin. And since measuring such risk factors as blood pressure and cholesterol only add cost while unnecessarily restricting treatment, they don’t envision involving physicians. That way, the Polypill proponents believe, their approach could save innumerable lives at a manageable cost, particularly because many of the drugs they would prescribe are, or soon will be, off patent.

For a tool that’s supposed to eliminate virtually all heart disease and stroke, the Polypill is a remarkably modest concoction. It combines what were once considered miracle drugs, but now are more or less taken for granted as effective means for reducing blood pressure and cholesterol levels. Those reductions have already translated into somewhat lower levels of cardiovascular disease. A 2001 paper in the *Journal of the American College of Cardiology* found that heart disease in the United States between 1981 and 1990 dropped by approximately 7% to 11%. More than half the improvement was attributed to a reduction in diastolic blood pressure, while 38% came from reduced cholesterol levels.

Eat, Drink and Be Healthy //

The Christmas issue of the *British Medical Journal* is known for its tongue-in-cheek articles, and in December 2004, 18 months after the journal launched the Polypill debate, epidemiologist Oscar Franco proposed a “Polymeal.” It replaces the five drugs of the Polypill with foods believed to have much the same impact on cardiovascular health.

Basing his choices on the medical literature, Franco nominated wine, fish, dark chocolate, fruits, vegetables, garlic and almonds, and suggested that eating them in sufficient quantities would reduce the risk of cardiovascular disease by 76%. For men, the diet increased life expectancy by 6.6 years, and for women, 4.8 years. “This is a theoretical model, just as the Polypill paper was, and you can say it was written with irony,” says Franco. “But it’s completely plausible. I think humankind should be given a choice.”

To Franco and other scientists, eating right and exercising regularly seems like a better idea than taking powerful drugs every day. “With or without the Polypill, people must improve their lifestyle,” says Robert Bonow, past president of the American Heart Association and current chief of cardiology at the Feinberg School of Medicine at Northwestern University. And the DASH (Dietary Approaches to Stop Hypertension) study has found that people who eat a diet full of fruits and vegetables and low in salt and saturated fat reduce their systolic and diastolic blood pressure by as much as if they had been taking blood pressure drugs.

Still, many researchers think preventing cardiovascular disease involves more than just skipping the cookies and going for a jog. It’s hard to make healthy lifestyle choices in today’s world, they argue, and often it’s only a privileged few who have the time and money to stay on the right path. “To greatly reduce the risk of cardiovascular disease, there need to be political, fiscal, environmental and structural changes at a societal level,” says Anushka Patel, one of the cardiologists conducting a Polypill trial in Australia. “Those aren’t things a doctor can directly address with a patient.”

Though encouraging, those gains don’t come close to what Nicholas Wald and Law believe is possible. Based on their review of trial data in the 2003 *BMJ* paper, they surmise that, taken long enough, a statin that cuts cholesterol by 1.8 millimoles per liter would reduce heart disease risk by 61%, while drops of 20 and 11 millimeters of mercury, respectively, in systolic and diastolic blood pressure, could push down heart disease risk by 46%.

Some experts dispute that analysis and maintain that statins would cut risk by only 35% and blood pressure drugs by 20%. But Wald and Law contend that statins don’t achieve their full effect until they’ve been taken for at least two years, and the duo’s 61% figure is for those who have crossed that threshold. They also assumed that the combination of three blood pressure drugs would have a greater impact than using

just one, because previous trials on multiple blood-pressure-lowering drugs show additive effects. The alternative analysis predicted a smaller effect, essentially the benefit of taking just one blood pressure reducer.

Whatever the correct calculation, real-world gains have been much smaller because most people don't achieve the necessary reductions in cholesterol and blood pressure. Despite effective therapies, only 34% of people with high blood pressure and 18% with high cholesterol have their conditions under control.

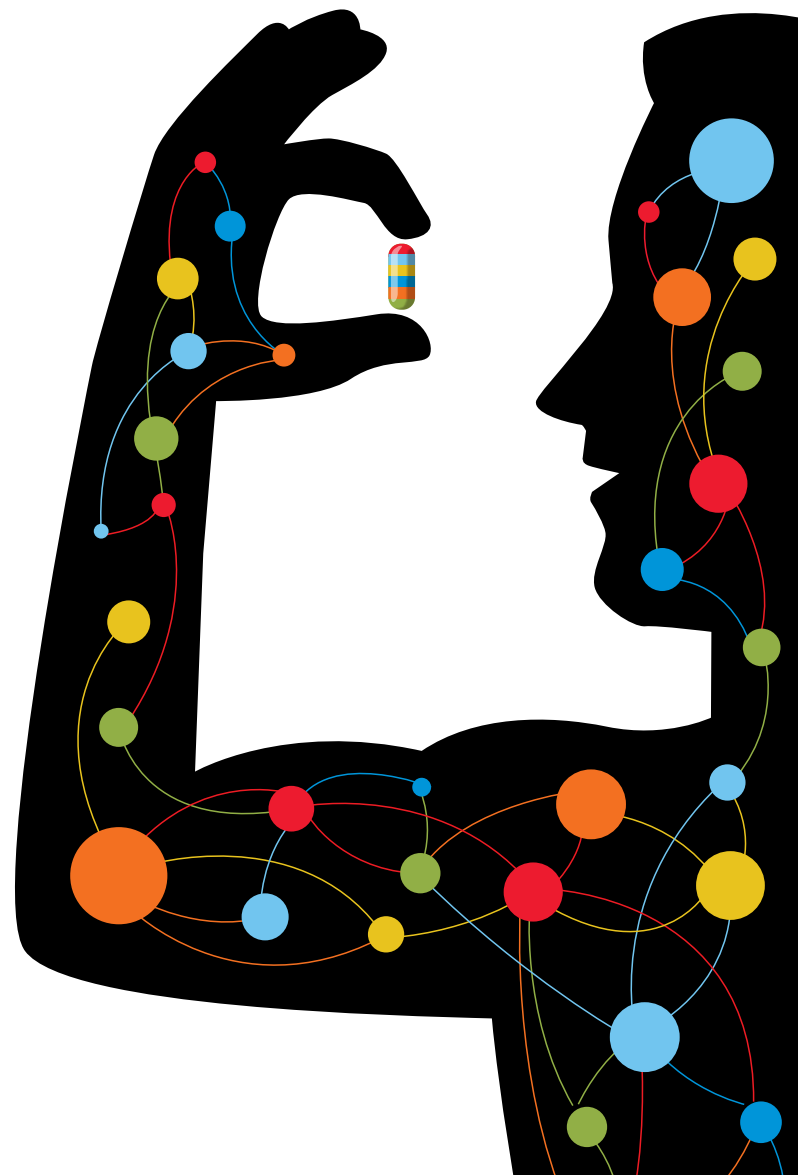
So, the first step in improving cardiovascular outcomes is to get everyone to take the drugs that could help them. According to generally accepted guidelines, candidates for treatment include anyone whose LDL cholesterol is higher than 100 or whose blood pressure is higher than 140/90. Wald and Law want to go further, giving statins and blood pressure medication even to people whose readings are below those levels but who are over age 55 because, they contend, a lifetime of exposure to our modern world elevates these levels to some degree, forcing everyone down the road to heart disease. Moreover, they say that combining the medication in a single pill will make it much more likely that people will stick to the regimen.

Other combination pills are already on the market, including one that brings together two asthma medications and another that combines three HIV drugs. To determine the best formula for the Polypill, Wald and Law went through a lengthy process detailed in the other papers published in the 2003 issue of the *BMJ*. First, they sifted through 354 randomized, double-blind, placebo-controlled trials of the five main categories of blood pressure drugs: thiazides (diuretics that prevent the kidneys from absorbing sodium); beta-blockers (which prevent substances like adrenaline from stressing the heart); angiotensin converting enzyme (ACE) inhibitors (compounds that block formation of angiotensin in the kidneys, thus relaxing arteries and promoting excretion of salt and water); angiotensin II receptor antagonists (which block receptors so angiotensin II cannot constrict blood vessels and thus increase blood pressure); and calcium-channel blockers (which keep calcium from entering heart and vessel walls, thus widening and relaxing vessels).

After reviewing the impact of these drugs alone and in combination, Wald and Law found that combining two or more produced a greater reduction in blood pressure than giving just one, while cutting the normal dose in half appeared to provide almost as great a benefit (80%) as the drugs at full strength. Extrapolating from the results of all the studies, they

hypothesized that if everyone over age 55 took a combination of three drugs at half the standard dose, there would be a 63% lessening of stroke risk and a 46% reduction in heart disease for people between the ages of 60 and 69.

Wald and Law performed a similar analysis of cholesterol-lowering drugs, examining 164 short-term, randomized, placebo-controlled trials on six statins: rosuvastatin, atorvastatin, lovastatin, simvastatin, pravastatin and fluvastatin. Those drugs reduce cholesterol by inhibiting the enzyme HMG-CoA reductase, thus slowing cholesterol production and increasing the rate at which it is cleared from the bloodstream. The team also examined 58 randomized trials of cholesterol reduction by any means and nine cohort studies (a type of observational study—not as rigorous as randomized, controlled trials), and they studied the effect of aspirin, which lowers risk of clots. Looking at 15 randomized trials, they concluded that low-dose aspirin reduces heart attacks by 32% and strokes by 16%.



After also considering side effects, Wald and Law proposed their Polypill formulation: a statin, the three blood pressure drugs at half dose, and low-dose aspirin. Such a pill, they calculated, may cause side effects in 8% to 15% of people—not a trivial risk, and mostly a result of aspirin. Certain people, such as those with asthma or those who are intolerant of aspirin, might experience more severe problems. Still, adding together the risk reductions each component part could be expected to produce, they projected that the Polypill could enable one-third of the population to live an average 11 to 12 years longer.

Although it's far from certain that would really happen, a few observational studies have looked at the long-term benefits of combining some of the components proposed for the Polypill, and the results seem to support Wald and Law's claims. In a German study, patients who had a heart attack and later took four different medications— aspirin, a beta-blocker, an ACE inhibitor and a statin—were significantly more likely

to survive one year than those who took zero, one or two medicines. Similarly, a British study found that a combination of statins, aspirin and beta-blockers reduced mortality more than any drug given by itself or with one other medication.

These are trials of secondary prevention, in people who are already sick, rather than the primary prevention that Wald and Law would like to see, and the trials are also observational studies, rather than the more rigorous randomized, controlled trials. Still, the Polypill's components have compiled years of effective treatment when used singly, and these studies add weight to the idea that a combination might produce even better results.

Several secondary prevention trials of the Polypill may soon begin validating the idea. In Australia and New Zealand, more than 1,000 people with cardiovascular disease will either be given a Polypill (in these trials, it consists of two blood pressure drugs, a statin and aspirin) or continue to be treated as usual by their doctors. One aim is to gauge whether they are more likely to stick to the drug regimen when the drugs are all in one pill. Another goal, cited in a report by a working group at the U.S. Centers for Disease Control and Prevention convened in early 2005 to discuss the Polypill, is whether the combination of drugs will prove to be additive ($I+I=2$), subadditive ($I+I>1$ but <2), antagonistic ($I+I<1$) or synergistic ($I+I>2$).

The Parts of Its Sum //

TRIALS IN AUSTRALIA AND NEW ZEALAND WILL TEST TWO POLYPILL TYPES AND SIX DOSAGE COMBINATIONS. HERE'S A BREAKDOWN OF ONE FORMULATION.

NAME	DOSAGE	FUNCTION	BENEFIT	SIDE EFFECTS
Simvastatin	10, 20 or 40mg	Lowers cholesterol by inhibiting the enzyme HMG-CoA reductase	May reduce heart disease risk by at least 25%	Rare instances of rhabdomyolysis and liver failure
Lisinopril	5 or 10mg	Blocks angiotensin in the kidneys, promoting excretion of salt and water	Together, may reduce heart attack risk by 15%–20%, stroke risk by 40%–50%	Among other effects, adverse levels of potassium and other substances in the blood
Hydrochlorothiazide	12.5mg	Diuretic that blocks kidneys from absorbing sodium		
Aspirin	75mg	Prevents platelets from forming clots	Reduces ischemic heart disease events by 32% and strokes by 16%	Poses the most serious risks, mostly because of hemorrhage
Polypill	Varies	May lower cardiovascular risks: may reduce blood pressure, reduce cholesterol and inhibit platelet function	May prevent more than 50% of heart attacks and strokes	Fewer than 5% of trial subjects likely to drop out because of side effects

All the trials will also look for adverse effects of taking drug combinations. The potential for such problems was a major issue for the CDC group, which was concerned about the possibility of aspirin producing serious adverse effects, mostly because of hemorrhage. Statins can also trigger serious side effects, including rhabdomyolysis (muscle breakdown) and liver failure from hepatitis, but problems are exceedingly rare—in the United States, rhabdomyolysis occurs at a rate of one per 10 million prescriptions, and in 13 years the Food and Drug Administration has recorded only 30 cases of liver failure because of statins. Side effects of the blood pressure drugs include cough, changes in sexual function and adverse blood levels of potassium, glucose and uric acid.

“We’re not certain yet—because we haven’t had any randomized, controlled trials—of the real side effects of putting all five drugs together,” says Lawrence Green, co-chair of the CDC panel. “But side effects are a potentially ominous issue, particularly if you’re not going to monitor people taking the pill.”

Still, if the secondary prevention studies find that the Polypill is both safe and an improvement over taking each drug individually, researchers could then move on to trials for primary prevention. The CDC group saw great potential in treating people before they’ve had cardiovascular problems, and the members were open to using the Polypill as its inventors envision, as an over-the-counter, safe-for-everyone pill.

“Is there sufficient benefit to be derived for the one-third of the population who will benefit to put two-thirds of people on a regimen that won’t do anything for them?” asks Green. “I would say yes—one-third of the population benefiting with minimal risk to the other two-thirds is very substantial.”

In Wald’s best-case scenario, the Polypill should be available for general use within 10 years. Getting such a complex combination drug approved in the United States could be difficult—drug patent laws in other countries are more liberal (or, in some cases, nonexistent), and the rules for drug trials also favor quick approval. Pharmaceutical companies in India are already making versions of the Polypill for the Australian and New Zealand trials, and many proponents of the drug combination, including the World Heart Federation’s Valentin Fuster, think developing countries are where the Polypill may do the most good.

According to the World Health Organization, some 80% of worldwide cardiovascular deaths now occur in low- or middle-income countries, and by 2010 cardiovascular disease will be the leading cause of death in developing nations, thus

overtaking communicable diseases. An inexpensive, widely available Polypill that requires few medical resources might be particularly helpful in those parts of the world.

In the United States, patents have already expired or will soon lapse on many of the drugs, making it easier to combine them into one pill, but the FDA will still require trials to determine whether the combined drugs are safe and at least as effective as taking them individually. And all of this assumes there will be drug companies interested in developing Polypill drugs from generic components that may not generate large profits. But if the drug eventually is taken by a significant fraction of the world’s population, the benefits could be huge.

Here’s how Wald and Law sum it up in their original paper: “The preventive strategy outlined is radical. But a formulation that prevented all cancer and was safe would undoubtedly be widely used, and one that prevented more than 80% of cardiovascular disease would be even more important, because such deaths are more common than cancer deaths. It is time to discard the view that risk factors need to be measured and treated individually if found to be ‘abnormal.’ Instead it should be recognized that in Western society the risk factors are high in us all, so everyone is at risk; that the diseases they cause are common and often fatal; and that there is much to gain and little to lose by the widespread use of these drugs.”

Now, with a spate of trials beginning, the team members are confident their Polypill is about to be validated. Someday soon, they believe, it could prevent thousands of needless deaths each year. ■

→ DOSSIER

1. “A Strategy to Reduce Cardiovascular Disease by More Than 80%,” by N. J. Wald and M. R. Law, *British Medical Journal*, June 28, 2003. In the paper that kicked off the controversy, Wald and Law make the kind of grandiose claims that staid scientific papers typically eschew.
2. “The Polymeal: A More Natural, Safer, and Probably Tastier (Than the Polypill) Strategy to Reduce Cardiovascular Disease by More Than 75%,” by Oscar Franco et al., *British Medical Journal*, December 18–25, 2004. With stern warnings against possible adverse effects of the Polymeal (garlic could ruin a romantic rendezvous, redundant cardiologists could be retrained as Polymeal chefs), this satirical yet scientific paper is an enjoyable read.
3. “The Polypill: At What Price Would It Become Cost Effective?” by Oscar Franco, Ewout Steyerberg and Chris de Laet, *Journal of Epidemiology and Community Health*, March 2006. Franco is back—this time calculating the maximum annual price at which the Polypill would be cost-effective as a primary prevention of cardiovascular disease. The finding: \$389 to \$528 per high-risk man aged 50 to 60 years.