

**Battle of nerves:**

After Syria attacks, scientists seek better sarin antidotes

**Change of heart:**

Budget cuts loom for the Framingham Heart Study

**New formula:**

Techniques in process chemistry enable cheaper HIV drugs

Polypill improves adherence but fails to win all scientists' hearts

Nicholas Wald's flash of insight came about 15 years ago. While recovering from a serious illness at his wife's family's house in New York, he watched as his father-in-law swallowed multiple pills each day to treat his cardiovascular disease. "I thought, my goodness, the combined effect of these pills is very large, but the problem is they should have started giving them 30 years ago as a preventative treatment," recalls Wald, an epidemiologist at the Wolfson Institute of Preventive Medicine at Barts and The London School of Medicine and Dentistry in the UK.

In 2003, a few years after his Eureka moment, Wald and his Wolfson colleague Malcolm Law published a statistical analysis suggesting that rolling a statin, an aspirin, a B vitamin and three blood pressure-lowering drugs into a single so-called polypill would slash the number of heart attacks and strokes by more than 80% if given to everyone over 55 years of age (*BMJ* **326**, 1419–1424, 2003). The study caused a stir: detractors said it strongly overstated the treatment's benefits and bemoaned the medicalization of society, while supporters insisted that the population at large was indeed sufficiently at risk to justify such wide uptake.

That debate has raged on ever since, with little clinical data involving people with established heart disease to inform the discussion. However, last month an international consortium published the results from the first polypill trial involving high-risk individuals. The UMPIRE trial—short for use of a multidrug pill in reducing cardiovascular events—enrolled around 2,000 people in India and Europe who had already experienced heart attacks or strokes. It found that 86% of study participants given a four-in-one polypill stayed on their medication, compared to only 65% of those who received standard care, which includes taking multiple pills separately (*JAMA* **310**, 918–929, 2013). The study also demonstrated that people taking the polypill experienced slightly greater improvements in blood pressure and lipid profiles.

Such patients with histories of cardiovascular disease are perfect candidates for the polypill, says Simon Thom, a cardiologist at Imperial College London who led the UMPIRE study. "They're the low-hanging fruit of the prevention populace." Similar results were previously observed in Indian people between the ages of 45 and 80 without established heart disease but with a correlated risk factor such as diabetes (*Lancet* **373**, 1341–1351, 2009).

What's still unproven is whether the improved adherence seen in people taking a polypill translates to fewer heart attacks and strokes in the long run. "I think most people, myself included, would like to see the data that it's likely to lead to a better [clinical] outcome," says Robert Bonow, a cardiologist at the Northwestern University Feinberg School of Medicine in Chicago who has not been involved in any polypill studies.

A five-year trial of 8,000 people in ten low- and middle-income countries, launched last year by Salim Yusuf, of McMaster University in Hamilton, Canada, and his colleagues, will be the first to address this question. In such populations, where the drugs are often less available or unaffordable and where high-risk individuals often aren't getting any medicine at all, such a pill can be highly effective, Bonow predicts. "That's where the polypill has its sweet spot," he says. But in wealthier populations, a one-size-fits-all approach falls short. It's much better for patients to see a clinician who can titrate the best dose of each drug, he contends.

Better than nothing

Views like that will be a major hurdle to a polypill's acceptance by the medical establishment, expects Anthony Rodgers, a global health researcher at the University of Sydney who was a co-author of the UMPIRE trial and has run several other polypill studies worldwide. "Specialists say, 'This is really bad medicine. I want people to be on the highest dose of the best statin and the best blood pressure medicine,'" he says. But, as Rodgers points out, adherence is a huge issue in wealthy countries, too. Patients



Take to heart: One pill for prevention?

on multiple medications often simply stop taking them. "At the end of the day, taking something is better than taking nothing."

The original populists of the polypill concept, for their part, have steadily moved forward. In June, Wald, Law and others began selling their pill directly to consumers through a company they cofounded called Polypill Ltd. After an online consultation with doctors at the website polypill.com, people in the UK over 50 years of age can receive a prescription to buy the polypill under the brand name PolyTor for £1.05 (\$1.68) per tablet. This pill contains four ingredients: simvastatin to lower cholesterol and low doses of hydrochlorothiazide, losartan and amlodipine to reduce blood pressure. Since all the components are widely used medicines to treat heart disease, physicians can prescribe the pill off label for preventative use, with a compounding pharmacy making the four-in-one formulation. However, Wald says he would like to eventually receive market authorization so he and other doctors can offer the polypill more broadly.

For now, Wald concedes the most likely buyers are "the educated well," but he hopes to partner with public programs to make it more widely and more cheaply available. His philosophy is simple: "If one can prevent a first cardiovascular event," he says, "there won't be a second one to prevent. So primary prevention should be the priority."

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