Can the polypill save the world from heart disease?

The concept is simple. Several different drugs are available (generically and thus inexpensively) to treat many of the cardiac risk factors. So, combining them in one pill could reduce heart disease by 80%. This approach has obvious appeal, and vast implications for global health, because heart disease is the leading cause of death worldwide. The Indian Polycap Study (TIPS), reported in *The Lancet* today, moves us one step closer to realising this dream.

TIPS is a large phase II randomised trial that assessed the effects of nine different pills containing either single agents or combinations of two, three, four, or five (the polypill) drugs, to measure their effect on risk factors such as blood pressure and cholesterol concentrations, as well as the feasibility and tolerability of administering a single pill to a relatively unselected group of patients. The study was not a large outcomes trial to show that the polypill reduced mortality. The group of patients studied is one that has been increasing rapidly in numbers in the past decade with the increase in obesity across the world—middle-aged (45–80 years) men and women without previous cardiac disease, but with at least one cardiovascular risk factor: high blood pressure, obesity (measured by the hip to waist ratio), high cholesterol, diabetes, or smoking. Patients were recruited from 50 centres in India, a fitting reminder of the globalisation of both the burden of heart disease and of clinical trials aimed at reducing such burden.

The results from TIPS show that each of the components of the polypill did what was intended: the statin reduced cholesterol, the three antihypertensives reduced blood pressure—and the more of them, the greater the reduction—and aspirin reduced the clotting ability of the blood. They found one unexpected issue with the Polycap: the degree of cholesterol lowering was slightly less with the Polycap than in patients who got simvastatin alone. This effect seems to be related to the rate of conversion of simvastatin in the Polycap. This finding highlights the importance of a phase II study such as TIPS to identify any such issues with the polypill, before testing in a large outcomes trial. Also, in view of the safety and tolerability in large trials of simvastatin 40 mg, the next generation polypill might shift to that higher dose (or to a moderate dose of a more potent statin which should become available generically in a few years).

A key and very promising finding from TIPS was the tolerability of the Polycap. Although the rates of discontinuation were higher than one might have anticipated in a 12-week study (about 15%), much of it was apparently due to social reasons and patients refusing treatment. There was, however, not a significantly higher rate overall of discontinuation with the Polycap compared with the other combinations. Some regimens seemed to be a little better tolerated, and those with triple antihypertensives had a slightly higher rate of hypotension (as would be expected). On the other hand, some components of the polypill might help counteract side-effects of others (eg, potassium concentrations for the angiotensin-converting-enzyme inhibitor and the diuretic). Fortunately the absolute rate of drug-specific discontinuations was low, which means that the overall feasibility and tolerability of the polypill approach does seem to work. Interestingly, if we recall that the patients had to have only one risk factor to participate in the trial (eg, hypertension, diabetes, smoking), all patients had all risk factors treated. So a smoker without a history of high blood pressure or high cholesterol was nonetheless treated for both, and was able to tolerate the treatment. This approach illustrates the feasibility of the principle that one can treat patients with multiple classes of drugs for cardiovascular risk factors, even if the patients do not have some of these risk factors.
What are the challenges? First, we need a large phase III trial with longer follow-up to assess the true feasibility of this strategy. How can the use of a polypill be implemented in a broad population? What is the full safety profile (there were 3–8% of patients who had increases in creatinine and potassium and in liver function tests; what adjustments need to be made to those patients?). Do they stop the polypill if one component causes a side-effect? How does the doctor decide which component caused the side-effect? Second, we would also like to have a large outcomes trial, to document a reduction in death, myocardial infarction, and stroke with the polypill approach compared with current practice.

Third, there is the issue of dose, which is a fascinating difference from current practice. The Polycap had just one dose (generally a moderate dose) of each agent. Currently for combination pills, regulatory authorities require that the pill be available in every dose combination of each drug, so the combination pill would not limit treatment. However, this approach would obviously not be feasible with a pill with five or six components and each having two to four doses (which would lead to more than a hundred strengths of the polypill). Thus what is designed to be a simple pill would turn into a complicated prescribing morass. It might be feasible to consider having two or three broad strengths with some different doses of some components (eg, the antihypertensives) or there could be versions with only some components of the polypill that would, for example, have fewer antihypertensive drugs. That approach might help when treating a patient with only single risk factors (eg, a smoker without high blood pressure). Should such a patient be put on three antihypertensives, and thus have the risk of angio-oedema, glucose intolerance, or bradycardia?

A final challenge: would the availability of a single magic bullet for the prevention of heart disease lead people to abandon exercise and appropriate diet? Would this make two of the major root causes of heart disease worse? Hopefully not, but the medical profession would need to help ensure that this would not happen.

Where would this polypill fit into current medical practice? The major appeal is its simplicity and (presumed) low cost, which could improve compliance. Such appeal could have broad applicability in areas of the world with less access to medical treatment, where just one or two interactions with medical professionals could be the start of treatment that could lead to long-term cardiovascular prevention. But the polypill could also fit well into more modern medical systems, in which large proportions of patients with risk factors are untreated. If all these patients knew they could simply take their polypill, they might be more receptive to it—and as such vastly broaden the number of patients who might benefit from drugs that had been proven in multiple trials to reduce cardiovascular disease and mortality. Although TIPS does not provide all the answers, the study does take a first and crucial step forward and raises hope that, in conjunction with other global efforts to improve diet and exercise, the polypill could one day substantially reduce the burden of cardiovascular disease in the world.

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1 The Indian Polycap Study (TIPS). Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. Lancet 2009; published online March 30. DOI:10.1016/S0140-6736(09)60611-5.
3 Lee JK, Grese KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. JAMA 2006; 296: 2563–71.