The polypill concept
Nicholas J Wald, David S Wald

“Polypill” describes a fixed dose combination pill containing several components designed to lower several cardiovascular risk factors simultaneously. For people who have had a cardiovascular disease event or related disorders such as angina pectoris, combination treatment has been practised for many years, although apart from the use of aspirin there has been a tendency to treat each risk factor rather than the overall risk of the disease. For example, until recently statins have been prescribed only if serum cholesterol is raised. Blood pressure lowering drugs are given only if a diagnosis of hypertension has been made. This is inappropriate and leads to many people not receiving preventive treatment who could benefit from receiving such treatment.

EFFECT ON CARDIOVASCULAR RISK OF REDUCING SERUM CHOLESTEROL AND BLOOD PRESSURE
The basis for preventing clinical cardiovascular disease with a combination of agents that reduce causal risk factors is that, within the range of values of these risk factors in the population, there is no threshold below which a reduction in risk factor ceases to confer a reduction in risk. Indeed, cohort (prospective observational) studies show that blood pressure and cholesterol exhibit a linear relation between the level of the risk factor and the risk of the disease when the risk of the disease is plotted on a proportional (that is, logarithmic) scale. This relation has great clinical significance, because it shows that for given changes in the risk factor there is a constant proportional change in the risk of disease. So, for example, a reduction of 1 mmol/l in low-density lipoprotein (LDL) cholesterol is associated with an approximate 40% reduction in the risk of having an ischaemic heart disease (IHD) event, and a 10 mm Hg decrease in diastolic blood pressure is associated with an approximate 60% decrease in risk of stroke. Table 1 shows this. Meta-analyses of randomised trials have confirmed that these estimates derived from epidemiological cohort studies accurately predict the preventive effect of blood pressure and low-density lipoprotein (LDL) cholesterol-lowering drugs. They show that the effect of reducing LDL cholesterol on reducing the risk of an IHD event or stroke is near maximal after 2–3 years of starting treatment with a statin and the effect of blood pressure lowering therapy is maximal within a few weeks of starting treatment with blood pressure lowering drugs.

The estimated preventive effect of different changes in LDL cholesterol or diastolic blood pressure can be easily calculated: a 2 mmol/l reduction in LDL cholesterol would change the relative risk shown in table 1 by a factor of 2, but because of the proportional relation, the 2 is a power function (not a product), so the new relative risk is $0.6^2$—that is, 0.36 (not 0.6/2 or 0.50). The calculation is based on the relative risk and then converted into a percentage risk reduction, so a 2 mmol/l LDL cholesterol reduction (calculated relative risk of 0.56) translates into a risk reduction of 64%. Similarly an LDL cholesterol reduction of 0.5 mmol/l would reduce IHD risk by 23% (relative risk of 0.6$^{1.5}$ = 0.77—that is, a 25% risk reduction).

The magnitude of the reduction in the risk of disease by altering each of the two risk factors (LDL cholesterol and blood pressure) is substantial, and greater when they are combined. Epidemiological studies have shown that these two risk factors have independent effects on the diseases they cause and randomised clinical trials have confirmed this. Given this observation, it is simple to calculate the expected impact of reducing both LDL cholesterol and blood pressure simultaneously. Again this is calculated using the relative risks but, when estimating the combined effect of several risk factors, the relative risk estimates are multiplied together. In table 1 the combined effect of the specified reduction in LDL cholesterol and blood pressure on risk of IHD events is a relative risk of 0.6×0.6—that is, 0.36, or a reduction in disease of 64%. For stroke this is 0.9×0.4 which, coincidentally, is also a relative risk of 0.36, a 64% reduction.

SELECTING INDIVIDUALS FOR PREVENTIVE TREATMENT
For decades the clinical goal has been to “normalise” causal risk factors if they were judged too high or too low. Why reduce serum cholesterol if it was not elevated? Similarly, why reduce blood pressure if it was not judged to be high? The reason is that most events occur in people with levels of blood pressure and cholesterol in the middle of the risk factor distributions even though risk will be

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Approximate relative risk and percentage risk reduction from ischaemic heart disease events and stroke according to specified reduction in LDL cholesterol and diastolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in risk factor</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td></td>
<td>Relative risk</td>
</tr>
<tr>
<td>1 mmol/l LDL cholesterol</td>
<td>0.6</td>
</tr>
<tr>
<td>10 mm Hg diastolic BP</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Correspondence to: Professor N J Wald, Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, Charterhouse Square, London, UK, n.j.wald@qmul.ac.uk
higher where blood pressure or cholesterol is in the upper tail of the distribution.\textsuperscript{19, 20} Measuring LDL cholesterol and blood pressure, and then limiting treatment to those with high levels denies prevention to the bulk of the population who will experience most heart attacks and strokes.

Selection of people for treatment to lower cardiovascular risk factors should not, therefore, be based on the level of these risk factors, even though this sounds counter-intuitive. Selection should aim to identify all people who, in the absence of treatment, are at risk of developing a cardiovascular disease event. In those who have not already had a cardiovascular disease event, this risk is dominated by one factor alone—a person’s age.

Figure 1 shows the risk of a cardiovascular disease event in Britain plotted against age, based on incidence data collected by cardiovascular disease registries.\textsuperscript{21} The range of risk from age 25–75 is about 130-fold. The range of risk across the top and bottom quintile groups of the distribution is equivalent in screening terms to a test that has a 40% detection rate (or sensitivity) for a 5% false-positive rate.\textsuperscript{19} Combining many risk factors, each with poor discrimination, does not improve discrimination to any great extent.\textsuperscript{20} In general, it is disappointing but true that important causes of disease make poor screening tests.

THE PREVENTIVE TREATMENT

The effect of preventive treatment was described in three papers in the BMJ in 2008,\textsuperscript{13–15} based on a patent application filed in 2000.\textsuperscript{15} It was shown that a 1.8 mmol/l reduction in LDL cholesterol can be achieved by taking a daily statin, (for example 40 mg of simvastatin, 10 mg of atorvastatin or 5 mg of rosvastatin), and that the proportional reduction (about 37%) was independent of starting cholesterol.\textsuperscript{16} It was also shown that a 10 mm Hg reduction in diastolic blood pressure could be achieved with few and minor adverse effects by combining three blood pressure lowering drugs at half standard dose.\textsuperscript{17} The evidence was based on trials using different combinations of two drugs from different classes and estimates from these showed independent effects. Combining two classes of blood pressure lowering drug at half standard dose is about five times as effective in reducing risk as doubling the dose of a single drug.\textsuperscript{20} Recently, a randomised trial has confirmed the benefit of triple therapy over dual therapy.\textsuperscript{21}

A meta-analysis of 147 blood pressure lowering trials showed that all different classes of blood pressure lowering drug have similar degrees of efficacy that are almost entirely determined by their blood pressure lowering effect, with the exception of ß-blockers given immediately after a heart attack (which have a special effect over and above blood pressure reduction), and calcium channel blockers (which may have a somewhat marginally greater effect than other blood pressure lowering drugs in the prevention of stroke).\textsuperscript{18} The meta-analysis showed that the proportional risk reduction is the same in people with and without cardiovascular disease and is independent of starting blood pressure. Figures for this paper (available at bmj.com) show the contribution of the individual trials to the meta-analysis.

THE POLYPILL CONCEPT

While the polypill itself is a pill with a combination of agents that can reduce causal risk factors, the polypill concept goes further, and redefines the application and use of such a pill. It moves the polypill from being a formulation of convenience that may replace using several drugs in people who have had a cardiovascular event to its being used in the general population, offered to those at high risk of future disease on the basis of age alone. With full adherence to therapy, a polypill designed for primary prevention with four components (three blood pressure lowering agents and a statin) could reduce cardiovascular disease by about 75%. About one in three people taking the polypill would directly benefit from doing so, and each of these would, on average, gain 11 years of life without a heart attack or stroke.\textsuperscript{1}

It is now becoming generally accepted that the use of statins to lower cholesterol is worthwhile in people at increased risk of a cardiovascular disease event, regardless of the starting cholesterol level and that, in the absence of a history of cardiovascular disease, age is the main determinant of risk. It follows that a cholesterol measurement is not needed to initiate treatment; age alone is enough. Similarly, above a certain age, say 50 or 55, blood pressure should be lowered in everyone and measured in some, not measured in everyone and lowered in some, as is current practice.

The polypill concept is one in which pharmacoprevention is applied generally to a healthy population to prevent them from becoming patients—to prevent first cardiovascular disease events. If a first event is prevented, there is no second to prevent. Primary prevention should be the priority—its efficacy will substantially diminish the need for secondary prevention.

The professional response to the polypill concept in 2005 was mixed, often generating strong views of an over-simplistic approach that would undermine the practice of medicine. There were over 100 online “rapid responses” to the BMJ.
paper. The “one size fits all” approach would, in the opinion of some commentators, fail to “tailor” treatment to the needs of individuals. These concerns are not justified because with preventive treatment that achieves about a 75% reduction in disease, altering a component of drugs or altering the dose, will have a small impact on efficacy. Some people will not tolerate the polypill, and they will need to seek medical attention in order to find a more tolerable alternative. More than one polypill will be needed. For example, it is appropriate to include aspirin in a polypill for secondary prevention but not, on current evidence, in a polypill for primary prevention. While there is uncertainty over the value of folic acid and a lack of evidence of benefit from trials of folic acid and coronary heart disease, it would be reasonable to exclude it, but the evidence of a protective effect on stroke is greater, and this may weigh in favour of its inclusion.

FROM CONCEPT TO REALITY

There is no scientific doubt that a polypill with at least four components (three blood pressure lowering agents and a statin) could safely prevent most cardiovascular disease events. The challenge will be to bring such a pill to market in a regulatory environment that tends to be against the use of combination pills. Evidence across many areas of medicine, such as in the treatment of HIV infection and tuberculosis, shows that such combinations can enhance efficacy and reduce toxicity, cost and complexity of producing and delivering treatment to those who need it.

Formulating the components into a single pill has been achieved by several companies, mainly in India, such as Cipla, Dr Reddy’s Laboratories and Cadilla. One polypill (Polycap) has been used in a factorial trial to assess the impact on risk factor reduction. A source of uncertainty in bringing a polypill to market in Europe and North America is meeting the regulatory requirements for such a pill. Obtaining a product licence on the basis of bioequivalence between a polypill and its components used separately is one route to market, but this would limit the indications of use to those already granted in respect of the separate components. Thus, for example, a four-component polypill with three blood pressure lowering drugs and a statin would be assessed in bioequivalence studies with the separate components for use in patients who have both hypercholesterolaemia and hypertension. While this would allow the formulation to be sold, and therefore prescribed, the limited indication for use would be far removed from the polypill concept—to be used in healthy people regardless of their blood pressure or cholesterol levels.

Doctors could prescribe such a polypill (off-label) but off-label commercial promotion would be prohibited. There is a need for the regulatory authorities such as EMEA, MHRA and FDA to be flexible in their assessment of a polypill consisting of well established drugs that have been used for more than 15 years with a sound evidence base on their efficacy and safety. Published trials have often used the components together, and all analyses that have been carried out demonstrate the same or similar effect in the presence or absence of treatment with other drugs—that is, pharmacological independence. It should therefore be possible for an appropriately formulated polypill to obtain a product licence for the primary prevention of cardiovascular disease in people above a specified age on the basis of existing information available in the scientific literature. Because cardiovascular disease is not a new epidemic, society has perhaps become complacent about introducing and licensing drug formulations that could largely prevent it.

Consideration needs to be given to how the public will obtain the polypill. The target group is healthy individuals who would choose to take a polypill to prevent becoming cardiovascular patients or dying prematurely. It would be perverse if they had to become patients and see a doctor before obtaining the treatment. The answer may be pharmacist prescribers, who, in the UK, are permitted to prescribe drugs either under a Patient Group Direction with the supervision of a medical practitioner or independently if they are appropriately qualified. Based on a few questions (age, use of existing medicines and medical history), the polypill could be prescribed to people above a certain age (say 55) without a previous history of cardiovascular disease and who are not taking any of the classes of drugs in the polypill or others that might interact with them.

The population impact of a primary prevention polypill will largely depend on how many people choose to take it. Initially this may be limited to a modest proportion of the eligible population, but the proportion is likely to increase as the approach becomes accepted. Some of those who start will stop. Preliminary evidence from the Polypill Prevention Programme being conducted from the Wolfson Institute of Preventive Medicine (a direct implementation of the polypill concept using the individual components) shows that about 10% of people do not continue, and some of these have indicated that it is because of the inconvenience of dispensing several pills and having to split some to secure the appropriate dosage.

Large as they are, the potential benefits of the polypill should not detract from the importance of reducing the underlying causes of cardiovascular disease in the community—a diet consisting of too much salt, saturated fat, sugar and alcohol, against a background of an increasingly sedentary lifestyle and persistent failure to reduce the prevalence of smoking. Only if major progress on this front were achieved would the case for the polypill concept be diminished. Until then it is perhaps the only general method of dealing with the commonest cause of death and illness throughout the world today.

Competing interests: NW jointly holds a European patent (EU1272220) for a combination pill for the prevention of cardiovascular disease (patent pending in USA and Canada) and together with DW has an interest in its development.

Heart 2010;96:1–4. doi:10.1136/hrt.2009.186429

REFERENCES

1. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003;326:1419–23

Heart January 2010 Vol 96 No 1
17. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20536 high risk individuals; a randomised placebo controlled study. Lancet 2002;360:23–33