A strategy to reduce cardiovascular disease by more than 80%

N J Wald, M R Law

Abstract

Objectives To determine the combination of drugs and vitamins, and their doses, for use in a single daily pill to achieve a large effect in preventing cardiovascular disease with minimal adverse effects. The strategy was to simultaneously reduce four cardiovascular risk factors (low density lipoprotein cholesterol, blood pressure, serum homocysteine, and platelet function) regardless of pretreatment levels.

Design We quantified the efficacy and adverse effects of the proposed formulation from published meta-analyses of randomised trials and cohort studies and a meta-analysis of 15 trials of low dose (50-125 mg/day) aspirin.

Outcome measures Proportional reduction in ischaemic heart disease (IHD) events and strokes; life years gained; and prevalence of adverse effects.

Results The formulation which met our objectives was: a statin (for example, atorvastatin (daily dose 10 mg) or simvastatin (40 mg)); three blood pressure lowering drugs (for example, a thiazide, a β blocker, and an angiotensin converting enzyme inhibitor), each at half standard dose; folic acid (0.8 mg); and aspirin (75 mg). We estimate that the combination (which we call the Polypill) reduces IHD events by 88% (95% confidence interval 84% to 91%) and stroke by 80% (71% to 87%). One third of people taking this pill from age 55 would benefit, gaining on average about 11 years of life free from an IHD event or stroke. Summing the adverse effects of the components observed in randomised trials shows that the Polypill would cause symptoms in 8-15% of people (depending on the precise formulation).

Conclusion The Polypill strategy could largely prevent heart attacks and stroke if taken by everyone at increased risk irrespective of the risk factor levels; intervention on several reversible causal risk factors together; and reducing these risk factors by as much as possible.

We describe a strategy to prevent cardiovascular disease based on these three principles and quantify the overall preventive effect. We show that a daily treatment, the Polypill, comprising six components, each lowering one of the above four risk factors, would prevent more than 80% of IHD events and strokes, with a low risk of adverse effects. This strategy would be suitable for people with known cardiovascular disease and for everyone over a specified age (say 55), without requiring risk factors to be measured.

Methods

We identified categories of drugs or vitamins used to modify LDL cholesterol, blood pressure, homocysteine, and platelet function. For LDL cholesterol, statins are the drugs of choice. For lowering blood pressure, we considered all five main categories of drugs: thiazides, β blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and calcium channel blockers. Serum homocysteine is most effectively reduced by folic acid; vitamins B-6 and B-12 have relatively small effects. Aspirin is the most widely used and least expensive antiplatelet agent.

The choices of statin and of the categories and doses of blood pressure lowering drugs were...
Table 1 Effects of the Polypill on the risks of ischaemic heart disease (IHD) and stroke after two years of treatment at age 55-64

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Agent</th>
<th>Reduction in risk factor</th>
<th>% reduction in risk (95% CI)*</th>
<th>Source of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>Statin†</td>
<td>1.8 mmol/l (70 mg/dl)</td>
<td>81 (51 to 77)</td>
<td>Law et al4</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Three classes of drug at half standard dose</td>
<td>11 mm Hg diastolic</td>
<td>46 (38 to 53)</td>
<td>Law et al20</td>
</tr>
<tr>
<td>Serum homocysteine</td>
<td>Folic acid (0.8 mg/day)</td>
<td>3 μmol/l</td>
<td>16 (11 to 20)</td>
<td>Wald et al6</td>
</tr>
<tr>
<td>Platelet function</td>
<td>Aspirin (75 mg/day)</td>
<td>Not quantified</td>
<td>32 (23 to 40)</td>
<td>Table A on bmj.com</td>
</tr>
<tr>
<td>Combined effect</td>
<td>All</td>
<td></td>
<td>68 (64 to 91)</td>
<td></td>
</tr>
</tbody>
</table>

LDL—low density lipoprotein.
*95% confidence intervals include imprecision of the estimates of both the agent reducing the risk factor and the risk factor reduction decreasing risk.
†Atorvastatin 10 mg/day, or simvastatin or lovastatin 40 mg/day taken in the evening or 80 mg/day taken in the morning.

The dose of folic acid was the minimum needed to ensure the maximum reduction in serum homocysteine.4,10,11 The long term effect of a specified absolute reduction in LDL cholesterol, blood pressure, and homocysteine expressed as the proportional reduction in the incidence of IHD events and stroke was taken from published sources that were based on systematic reviews of cohort studies.3,8,14-16 Cohort studies show long term effects because the observed differences in risk factors between individuals will have existed for decades.3 Predictions from the cohort studies on LDL cholesterol and blood pressure in preventing disease have been corroborated by results of randomised trials, and both cohort studies and trials have shown that a specified reduction in blood pressure or serum cholesterol produces a constant proportional reduction in risk that is independent of the initial value of the risk factor.1,3,14,15 The average age at which cardiovascular event occurred in the studies was around 60-65 years.

Platelet function is difficult to quantify, and there is inadequate evidence on its association with ischaemic heart disease and stroke. We therefore used direct evidence from randomised trials of the effects of aspirin on disease events. Since the necessary information on stroke and adverse effects with low dose aspirin was not available from published meta-analyses, we conducted one. The efficacy of low dose aspirin (50-125 mg/day) is similar to that of higher doses (160-1500 mg/day), so we analysed only trials of low dose aspirin. We identified trials of ≥6 months' duration from previous meta-analyses,6,7 from Medline (using the search term “aspirin” in all fields and publication type “clinical trial”), and the Cochrane Collaboration and Web of Science databases. This yielded 15 trials: four were in healthy adults, nine in people with a history of IHD, and two in people with atrial fibrillation. We determined the average proportional reduction in IHD events and stroke, and the prevalence and incidence of adverse effects.

We calculated the combined effect of changing the four risk factors (the effect of the Polypill) by multiplying the relative risks associated with each. We calculated the years of life gained without a heart attack or stroke if people without a previous cardiovascular event used the Polypill from age 55. We used a simple Markov model incorporating the probabilities of three factors—a fatal or non-fatal IHD event or stroke (from an analysis of registry data), dying from another cause (from 1999 England and Wales mortality data), and remaining alive without a vascular disease event—stratified by sex and age by year. We then estimated the numbers of events during each subsequent year of life for 100 men and 100 women, and compared these numbers with those calculated from otherwise identical groups not taking the Polypill. From this we determined the extra years of event-free life gained by taking the Polypill.

Results
Efficacy
Table 1 shows the effects of the individual agents. By use of statins, LDL cholesterol concentration can be reduced by an average of 1.8 mmol/L Atorvastatin 10 mg taken at any time of day or simvastatin or lovastatin 40 mg taken in the evening or 80 mg taken in the morning after about two years of treatment can reduce the incidence of IHD events at age 60 by an estimated 61%. Higher doses produce little further gain. The overall reduction in stroke from an LDL cholesterol reduction of 1.8 mmol/L is about 17%. This estimate takes account of the reduction in risk of stroke in people with and without existing vascular disease (35% v 11%), a difference which arises because a stroke in people with vascular disease is more likely to be thromboembolic, and statins prevent thromboembolic, but not haemorrhagic, stroke) and also takes account of the proportion of first strokes that occur in people with known vascular disease (25% v 25% of 35% plus 75% of 11% making 17%).

The five main categories of blood pressure lowering drugs (thiazide, β blockers, ACE inhibitors, angiotensin II receptor antagonists, and calcium channel blockers), and the individual drugs within the categories, produce similar reductions in blood pressure, given dose as a ratio of standard dose.26 A combination of three drugs from different categories in low dose has greater efficacy and fewer adverse effects than using one or two drugs in standard dose.26 The blood pressure reduction with three drugs in combination at half standard dose is about 11 mm Hg diastolic, reducing the incidence of IHD events by 46% and stroke by 63%.16,17

The maximum effect of folic acid, achieved at a dose of about 0.8 mg/day,10,15 lowers serum homocysteine by 3 μmol/l (about 25%) and reduces IHD events by about 16% and stroke by 24%.4

Figure 1 shows our meta-analysis of the 15 randomised trials of low dose aspirin (50-125 mg/day). IHD events were reduced by 32% and strokes by 16% (details in web table A). As with statins, aspirin may have a larger preventive effect in people with occlusive
vascular disease than in those without such disease; the three trials of people without disease indicate a non-significant 9% reduction in risk of stroke (web table A).

Table 1 shows that changing all four risk factors together reduces the risk of IHD events by 88% and stroke by 80%. These results are obtained from the product of the relative risk estimates relating to interventions on each risk factor, which is the complement of the proportion of events prevented; thus, preventing, say, 61% is equivalent to a relative risk of 0.39. The following example illustrates the calculation. The relative risks of an IHD event for the four interventions in table 1 are 0.39, 0.54, 0.84, and 0.66, the product of which yields a combined relative risk of 0.12 or an 88% preventative effect (if 100 people who would have had IHD events without intervention were treated, 86% and 74% without folic acid, 85% and 73% without one blood pressure lowering drug (two instead of three), and 83% and 77% without aspirin. So, for example, aspirin prevents 32% of IHD events when used alone but prevents only an additional 5% of the original number of expected events when added to the other components in the combination.

Table 2 shows the expected proportion of people who would avoid an IHD event or stroke by taking the Polypill from age 55 and, in those, the average number of event-free life years gained. The estimates take account of deaths from causes other than IHD and stroke. About a third of people taking the Polypill would benefit. On average each will gain 11-12 years of life free from a heart attack or stroke. The gain in life is substantial at all ages.

Adverse effects
Table 3 summarises the extracranial adverse effects of low dose aspirin from our meta-analysis of 15 randomised trials. Table 4 uses these data together with those published in our companion papers11 to show the proportions of people reporting symptoms attributable to any of the components of the Polypill (percentage with symptoms in treated groups minus percentage in placebo groups in trials). If we included the three classes of blood pressure lowering drugs with the lowest prevalence of adverse effects (thiazide, angiotensin II receptor antagonist, and calcium channel blocker) in a Polypill formulation, 8% would be expected to have symptoms attributable to one or more of the six components of the pill, mostly due to aspirin. If we used the three least expensive blood pressure lowering drugs (a thiazide, a β blocker, and an ACE inhibitor) instead, a Polypill including these would cause symptoms in about 15% of people taking the pill.

Of all the components, aspirin has the most serious adverse effects, mainly due to haemorrhage (table B on bmj.com). In our meta-analysis of the trials of low dose aspirin the increase in haemorrhagic stroke (table A on bmj.com) was exceeded by the reduction in thrombotic strokes, producing an overall 16% reduction in stroke. There was no excess risk of fatal extracranial haemor-
rhage, with 13 and 15 deaths in the aspirin and placebo groups respectively in about 17 000 people in each (table B on bmj.com), and an excess risk of major non-fatal extracranial haemorrhage (mainly gastric) of 1.2 per 1000 person years (see table 3).

### Discussion

The Polypill strategy, based on a single daily pill containing six components as specified, would prevent 88% of heart attacks and 80% of strokes. About 1 in 3 people would directly benefit, each on average gaining 88% of heart attacks and 80% of strokes. About half of all cardiovascular deaths occur in individuals with a previous myocardial infarction or cerebral thrombosis. All such individuals should be offered treatment to reduce the reversible risk factors and would benefit from the Polypill. Patients with angina pectoris, transient ischaemic attacks, peripheral arterial disease, and diabetes mellitus should also consider taking the Polypill.

Among people without existing disease, the most discriminatory screening factor is age. As 96% of deaths from ischaemic heart disease or stroke occur in people aged 55 and over, treating everyone in this group would prevent nearly all such deaths. Using different age cut-offs for men and women, or smokers and non-smokers, or combining several risk factor values with age and sex to produce individual estimates of overall risk would add little discrimination and would probably not justify the added complexity and cost. Figure 2 illustrates this with serum cholesterol, blood pressure, and serum homocysteine. These factors, though aetologically important, are poor predictors of future cardiovascular disease events. There is little separation between the distributions of the risk factors in people who over a specified period do or do not have a disease event. With such closely overlapping distributions there are no cut-off levels that include most people who will have disease events but few of those who will not have them. Cut-off levels that identify the 5% of the unaffected population who have the most extreme values of the risk factors identify only about 15% of the disease events (24% for blood pressure and stroke). The screening performance of cardiovascular risk factors in combination is little better.

### Table 3: Extracranial adverse effects of low dose aspirin (50-125 mg) from the meta-analysis of 15 randomised trials

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No of events*</th>
<th>Excess risk (treated minus placebo) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin group</td>
<td>Placebo group</td>
</tr>
<tr>
<td>Extracranial haemorrhage:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal bleed</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Non-fatal major bleed (required transfusion or surgery)</td>
<td>51</td>
<td>28</td>
</tr>
<tr>
<td>Haematemesis or melaena</td>
<td>199</td>
<td>98</td>
</tr>
<tr>
<td>Any bleed</td>
<td>1049</td>
<td>710</td>
</tr>
<tr>
<td>Upper abdominal discomfort, including heartburn</td>
<td>689</td>
<td>621</td>
</tr>
<tr>
<td>Any symptom (any bleed and abdominal discomfort)</td>
<td>1738</td>
<td>1331</td>
</tr>
<tr>
<td>Adverse effects sufficient to stop taking the tablets</td>
<td>482</td>
<td>438</td>
</tr>
</tbody>
</table>

*Numbers of participants in the aspirin and placebo groups of each trial were almost identical (see web table B).

### Table 4: Prevalence of participants in randomised trials reporting symptoms attributable to the Polypill components (in doses specified in table 1)

<table>
<thead>
<tr>
<th>Drug or vitamin</th>
<th>% of participants with symptoms*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any symptoms</td>
<td>Symptoms sufficient to stop treatment in short term trials</td>
</tr>
<tr>
<td>Statin†</td>
<td>0.1</td>
</tr>
<tr>
<td>Thiazide‡</td>
<td>2.0</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonist§</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Calcium channel blocker¶</td>
<td>1.6</td>
</tr>
<tr>
<td>Folic acid</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Aspirin (see table 3)</td>
<td>3.9</td>
</tr>
</tbody>
</table>

*Percentage in treated group minus percentage in placebo group.
Adverse effects
The Polypill may not be suitable for some people. β blockers are unsuitable for people with asthma, and some people are intolerant of aspirin. Monitoring to prevent rare serious adverse effects of treatment might be considered, measuring serum creatine kinase and transaminase (for rhabdomolysis and hepatitis caused by statins) and serum potassium and creatinine (for acute renal failure caused by ACE inhibitors and angiotensin II receptor antagonists). However, the value of such monitoring is uncertain. The complications are rare, it is not known whether monitoring will avoid them, and the tests lack specificity, so the increased risk of cardiovascular disease after stopping the drug in people positive on monitoring may outweigh any benefit.

Cost and acceptability
A low cost Polypill could use generic components that are not subject to patent protection (simvastatin (from mid-2003), hydrochlorothiazide, atenolol, enalapril, folic acid, and aspirin). This formulation does not have the lowest rate of adverse effects, but even if about 10% of people were intolerant of the formulation it would still have considerable public health merit. Those found to be intolerant could be prescribed alternatives to avoid the side effects. Controlled trials of different formulations of the Polypill would provide direct estimates of acceptability.

Conclusions
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 recognised 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. No other preventive method would have so great an impact on public health in the Western world.

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Contributors: The paper was written by NW and ML. NW generated the idea for the Polypill, which was developed jointly with ML. NW is guarantor.

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Competing interests: The authors have filed a patent application on the formulation of the combined pill described here (application Nos GB 0100548.7 and GB 008791.6, priority date 10 April 2000) and a trademark application for the name Polypill.

Factors associated with adverse outcomes relate to recognised national shortages of midwives, inadequate fetal monitoring, and poor interpretation of cardiotocographs in birth asphyxia cases.

Further problems are failure to respond to cardiotocographic abnormalities and delay in summoning medical assistance and involving senior staff.

Adverse events occur as a result of midwifery staffing shortages; “near misses” due to staffing shortages occur frequently and remain unreported.

Poor skill mix of midwives exists at times, and midwifery shortages prevent uptake of opportunities for training or updating.

No contingency plans existed in any of the units to cope with the unexpected surges in demand for care that occur frequently on labour wards. During intensely busy periods, when shortfalls were most acute, senior midwives in charge of the shift were unable to provide support for inexperienced midwives.

Unless protected time is provided for midwives for training in interpretation of cardiotocographs and emergency obstetric management, training during working hours will remain low owing to staffing shortages. Implementation of information technology has also increased the midwifery workload, and we suggest that clerical aspects of midwives’ work could be delegated.

Although team midwifery systems may meet the challenges of Changing Childbirth, relatively inexperienced midwives occasionally have to work in an intensive care situation on the labour ward with high risk cases. When such work is sporadic, the development of necessary skills becomes very difficult, creating stress for the midwife and risk for the client. Skill mix within the labour ward also depends on cover provided from other teams, but independent planning of duty rosters means that overall labour ward skill mix becomes less predictable.

Consideration should be given to whether the risks generated by team midwifery systems outweigh the benefits of attempting to provide continuity of care.

Conclusion

We observed many latent failures (“accidents waiting to happen”) in this study. Inadequate midwifery staffing levels and ineffective deployment of midwives remain essential failings in the system of care and are the foundation of many adverse events and “near misses.”

Contributors: See bmj.com

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Competing interests: None declared.

Ethical approval: The North West multicentre research ethics committee approved the study, as did each of the seven trusts’ local research ethics committees.


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