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DOI: 10.1136/bmj.330.7499.1035

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The polypill and cardiovascular disease

May be appropriate for secondary, but perhaps not for primary prevention

The prevention of cardiovascular disease with drug therapy is well known. Randomised controlled trials and meta-analyses of trials of lipid and blood pressure lowering and antiplatelet therapy have established their efficacy in the prevention of cardiovascular diseases. Wald and Law have proposed that these three treatments, along with folic acid, be combined into a “polypill.” They propose a combined strategy for primary and secondary prevention—targeting all people with pre-existing cardiovascular disease (secondary prevention) but more controversially, targeting all adults aged over 55 (primary prevention) as well. The underlying assumption concerning the efficacy of this strategy is that the six individual ingredients of the polypill (thiazide diuretic, angiotensin converting enzyme inhibitor, β blocker, statin, aspirin, and folic acid) when combined together have synergistic treatment effects—calculated by multiplying the relative risk reductions on each class of treatment. Their polypill strategy has generated worldwide interest, with some critics questioning this underlying multiplicative assumption as being too optimistic.

For these reasons, the paper by Hippisley-Cox and Coupland in this issue (p 1059), examining the individual and combined effects of three of the polypill ingredients—statins, aspirin, and blood pressure lowering drugs—is timely. Their analysis provides support for the synergic action of the polypill in the context of secondary prevention of coronary heart disease. Their analysis of 11 330 patients with coronary heart disease shows that all cause mortality is lower in those patients taking drug combinations—two or three drugs when compared with those taking single agents. These findings are consistent with a previous study that showed that a combination of two drugs, aspirin and pravastatin, is superior to either drug alone in the secondary prevention of cardiovascular disease. A further study of dispensed prescribing in the secondary prevention of coronary heart disease in 4892 patients in Tayside, Scotland, also shows that patients taking an additional cardiovascular drug experience fewer cardiovascular events than patients taking statins alone, but that this synergistic effect was not sustained when two additional drugs were taken: hazard ratios for combinations of two and three drugs were the same. Overall these studies provide support for the synergistic effects of two, but not three or four, drug combinations in secondary prevention. However, these studies are non-randomised comparisons of outcomes and are therefore prone to confounding by severity of disease and other factors.

In the context of primary prevention many uncertainties remain. Recent evidence concerning the differential effect of aspirin in women compared with men is emerging. While the efficacy of aspirin in men is established, the recently completed women’s health study, of low dose aspirin (100 mg every other day) compared with placebo, did not produce a reduction in all cause mortality or fatal and non-fatal myocardial infarction. Although observational evidence favours a possible causal association between raised plasma homocysteine concentrations and cardiovascular disease, this association has been described as modest; a 25% reduction in usual homocysteine concentrations is associated with a 11% lower risk of coronary heart disease and a 19% lower risk of stroke. We have growing evidence from approaches using mendelian randomisation that the expected effects of the folic acid component may not be confirmed. Furthermore, a recent randomised trial of 2.5 μg/day of folic acid (the proposed polypill dosage is 0.8 μg/day) was not associated with a reduction in the combined trial end point of stroke, coronary events, and death in patients who has previously had a cerebral infarction. In the light of conflicting evidence between observational and randomised controlled studies concerning the benefits of antioxidant vitamins and prevention of cardiovascular disease, caution is needed before extrapolating the benefits from observational studies to benefit from treatment with the folic acid component of the polypill.

Other concerns about the primary prevention strategy of the polypill relate to its non-specific scatter-shot primary prevention approach, which would expose people at lower risk to lifelong treatment, with attendant medicalising of the population. Cost effectiveness analyses that estimated the impact of cardiovascular risk in the strategy to treat hypertension have shown that treating individuals at high risk is highly cost effective, irrespective of age or sex. However, individuals at lower risk (who represent most of the adult population) are much more expensive to treat in terms of gain in quality adjusted life years. Furthermore, the preference of patients has a strong bearing on the cost effectiveness of treatment in these low risk individuals.

The underlying tenet of the polypill—that combination therapy is better than monotherapy—may well be correct, particularly with regard to secondary prevention of cardiovascular disease. Hippisley-Cox and Coupland’s paper goes some way in providing data concerning the effects of combined treatment in
secondary prevention of coronary heart disease. In terms of primary prevention, development and testing of combination pills aimed at reducing more than one risk factor seems entirely logical, particularly in the context of assessment of global cardiovascular risk. Funding bodies and the NHS need to support the necessary trials and cost effectiveness studies to further examine the polypill strategy in comparison with non-pharmacological alternatives.

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Competing interests: None declared.

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