BMJ 2003;327:809-810 (4 October), doi:10.1136/bmj.327.7418.809-a

Letter

"Polypill" to fight cardiovascular disease

Authors' reply

EDITOR—Your correspondents overlook the extent of the health gain achievable with the "Polypill" and of the large amount of evidence underpinning our estimates of efficacy and adverse effects.[1]

About one person in three would benefit, and the Polypill would offer many people important extra years of active and useful life, with benefits evident over decades. The adverse effects, on the other hand, would mostly be apparent after a few weeks, in which case a variant of the pill could be substituted—for example, one without aspirin.

Of course, the Polypill is not an alternative to adopting a healthy lifestyle such as not smoking or not becoming overweight: it is a complementary means of prevention. We agree that work on the Polypill needs to continue so that after the necessary clinical trials it can be made available.

Ramos's view, that medicine should remain a patient based practice, is too limited; it would forgo important preventive measures such as vaccination. The motivation in seeking a patent for the Polypill is to help ensure its development and to fund the necessary clinical trials, which will be costly.

The expected 61% reduction in ischaemic heart disease events from statins is not twice that yet seen in any trial, as stated by Assmann et al and highlighted by White as a "spectacular claim." Randomised trials have shown this directly.

In all trials that lowered low density lipoprotein cholesterol by $\geq$ 1.5 mmol/l (on average 1.6) (see our table 6[2]) the average reduction in ischaemic heart disease events was 51% after two years of statin treatment. With a 1.8 mmol/l reduction the benefit will be greater, and evidence from cohort studies indicates a 61% reduction. Although individual blood pressure lowering drugs reduce ischaemic heart disease events by about 20%, the reduction will be greater when three drugs are used together in low dosage. Trials show an additive effect on blood pressure lowering (see our figure 3[3]), and the cohort studies show a greater reduction in disease events with greater reduction in blood pressure. Combining these two sets of data quantitatively yields the estimated 46% reduction in risk of ischaemic heart disease events.

The published estimates of cost per year of life saved by using statins summarised by Messori et al are too high for four reasons. The cost of simvastatin can be expected to fall since it has recently come off patent protection. The effect of statins in preventing heart disease has, in the past, been underestimated in trials and cohort studies as we described.[4] We propose that the Polypill be used without medical examination or blood tests, so these costs are largely avoided. It is more appropriate to consider years of life gained free from a heart attack or stroke, rather than simply years of life gained. If the daily cost of the Polypill were about £1 the estimates summarised by Messori et al would be about eight times too high.

On 3 September there were 88 rapid responses to our papers on bmj.com. We classified 24 as positive, 41 as negative, and 23 as raising related side issues. The responses ranged from rating the work as Nobelian to regarding it as a joke. We were struck by the strength of negative feeling by doctors on the use of a daily pill to prevent major disease. The public seems to think otherwise. The CNN website asked, "Would you take the Polypill?" and 95% replied yes. As DePoy says in his tongue in cheek summary of the responses, some regard the Polypill as immoral, and some thought, illogically, that it might benefit the population as a whole but individual patients would be worse off on average.[5] White's summary concentrates on the hyperbole. She does not comment on the lack of scientific input to the debate but selects invalid assertions such as "lack of trial evidence," the work being based on "flawed Framingham study data," and she makes the incorrect assumption of "perfect synergy."

Your correspondents have not given reason or evidence against the concept of the Polypill. Many have not recognised the massive data available on the efficacy and adverse effects of the Polypill components or the evidence showing their independent effects which together form the basis of our estimates. The

fact that the expected health benefit is large is a reason for supporting it, not a reason for disbelieving it.

Nicholas Wald, *professor*

n.j.wald@qmul.ac.uk

Malcolm Law, *professor*, **Joan Morris**, *senior lecturer*, **Alicja Rudnicka**, *lecturer*, **Rachel Jordan**, *research assistant*

Department of Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, Barts and the London, Queen Mary's School of Medicine and Dentistry, University of London, London EC1M 6BQ

Competing interests: NW and ML have filed a patent application on the formula of a combined pill to simultaneously reduce four cardiovascular risk factors, as well as a trademark application for the name Polypill.

References

1. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326: 1419-24. (28 June.)[Abstract/Free Full Text]
2. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326: 1423-7. (28 June.)[Abstract/Free Full Text]
3. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003;326: 1427-31. (28 June.)[Abstract/Free Full Text]
4. Law MR, Wald NJ, Wu T, Hackshaw A, Bailey A. Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study. *BMJ* 1994;308: 363-6.[Abstract/Free Full Text]
5. DePoy JA. The nays have it. Electronic response to: A strategy to reduce cardiovascular disease by more than 80%. bmj.com 2003. bmj.bmjjournals.com/cgi/eletters/326/7404/1419#34902 (accessed 3 Sep 2003).

Related Articles

Polypill may be available in two years
Richard Smith
BMJ 2003 327: 0. [Full Text]

Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials
M R Law, N J Wald, J K Morris, and R E Jordan
BMJ 2003 326: 1427. [Abstract] [Full Text]

Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis
M R Law, N J Wald, and A R Rudnicka
BMJ 2003 326: 1423. [Abstract] [Full Text]

A strategy to reduce cardiovascular disease by more than 80%
N J Wald and M R Law
BMJ 2003 326: 1419. [Abstract] [Full Text]

Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study
M R Law, N J Wald, T Wu, A Hackshaw, and A Bailey
BMJ 1994 308: 363-366. [Abstract] [Full Text]

Rapid Responses:

Read all Rapid Responses

Selective use of evidence
Adam Jacobs
bmj.com, 3 Oct 2003 [Full text]

Polypill - An OverDose of Reality
William J Burke
bmj.com, 4 Oct 2003 [Full text]

Lost opportunities
Anne Savage
bmj.com, 8 Oct 2003 [Full text]

foolish or fabulous folate
Yan Press, MD, et al.
bmj.com, 23 Jul 2004 [Full text]