A cure for cardiovascular disease?

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Combination treatment has enormous potential, especially in developing countries

See *Papers* pp 1419, 1423, and 1427

Today's *BMJ* contains one of the boldest claims for a new intervention—"a greater impact on the prevention of disease in the Western world than any other known intervention."[1] Is it a new magic bullet for cancer or a new gene therapy? No, it is a new strategy to deliver some of our most well known medicines. Wald and Law propose that a single pill containing aspirin, a statin, three blood pressure lowering agents in half dose, and folic acid is provided to people with vascular disease and those aged over 55 years. They synthesise an enormous amount of information (including over 750 trials with 400 000 participants) to estimate that the pill would reduce heart disease and risk of stroke by over 80%, while causing symptoms warranting withdrawal of the pill in one to two per 100 and fatal side effects in less than one in 10 000 users. If this were correct the benefits would substantially outweigh hazards in people with vascular disease (who have more than a one in five chance of a major event over five years without treatment) and many others at higher risk.

Will the benefits be so great? All the components except folic acid have unequivocal evidence of benefits across the board, shown by randomised trials in different groups of patients. Large trials with folic acid are ongoing, and existing evidence is very encouraging. Lowering cholesterol concentrations that are above 4.0 mmol/l and blood pressure values above 120/80 mm Hg is likely to confer benefit[2] even though many early trials and much clinical practice focuses on people with hypercholesterolaemia or hypertension. Wald and Law argue convincingly that three blood pressure lowering agents at half the standard dose are the best way to achieve large reductions in blood pressure, which are the main, if not only, mechanism of benefit of these agents.[3] Since average levels of risk factors tend to be so far from optimal ones in developed countries, large reductions in risk factors are likely. However, at least among those without vascular disease the average effects may be less than the proposed 20/10 mm Hg and 1.8 mmol/l low density lipoprotein, leading to less marked risk reductions. None the less, one could reasonably expect more than a halving in cardiovascular risk in the first two years and a two thirds reduction in subsequent years. These joint effects are best estimated as the product of separate relative risks, since clinical trials show similar sized benefits from, for example, statins with and without aspirin. Wald and Law's combined estimates are consistent with previous ones.[4 5]

Will the side effects be so low? Contrary to many perceptions, these drugs have remarkably few side effects. Placebo controlled trials show that when people stop treatment it is rarely for pharmacological reasons. More information from trials on side effects from low dose combinations is clearly needed, especially before contemplating widespread use among people at moderate risk. However, common or serious unanticipated problems seem unlikely since these medications have been studied so extensively and used together so often.

What is needed to realise the potential benefits?

- Widespread debate on the new paradigm
- Technical solutions in developing and manufacturing the pill(s) so that chemical activity is maintained
- Explicit regulatory requirements, ideally based on balance of benefit and harm rather than principles that fixed dose polypharmacy is intrinsically undesirable
- Trials assessing bioavailability, intermediate endpoint effects, safety, tolerability, and adherence (clinical endpoint trials should not be needed for existing indications)[8]
- Ensuring those in need get access—clear indications and contraindications, affordable formulations and systems to ensure profits are made on large volumes rather than large margins

To whom should this new intervention be offered? The history of symptomatic vascular disease is least controversial, and the need is great—most such people are undertreated, even in developed countries,[6] despite being at highest risk. More controversial will be treating every person over the age of 55 although this debate should not detract from the size and certainty of net benefits in those with vascular disease. Age is of course the best proxy for exposure to life, and life in developed countries at present almost inescapably entails long term exposure to major risks, such as excess intake of salt and saturated fat. There are simple ways for more focused targeting of people at high absolute risk[7] that would entail treating far fewer people.

What is needed to realise the benefits of this approach? Key steps are outlined in the box, and some are expanded below.

Further debate is required among health professionals and regulatory authorities. Routine use of a "polypill" among, for example, survivors of ischaemic stroke would minimise undertreatment while at the same time reducing opportunities for tailoring

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(although that is still possible with different versions of the pill). Treating when benefit outweighs harm is accepted, but treating risk rather than risk factor thresholds is new. This strategy was proposed a decade ago,[7] and guidelines have developed that cross disciplines,[9] but traditional paradigms such as treatment of hypertension still predominate.

A wider debate is needed across society about extensive use of preventive medications, especially among people without symptomatic disease. Widespread uptake would require overcoming perceptions that cardiovascular disease is a "natural" cause of death, or one that does not lead to substantial disability. One must also bear in mind that a third or more of adults in many countries already take natural supplement pills regularly (mostly multivitamins with uncertain benefits, or antioxidants, now known to have no important benefits for major diseases). The strategy should be integrated with population wide approaches that address the root causes of cardiovascular disease, including reshaping societies so that smoking and development of life threatening levels of body fat, cholesterol, and blood pressure are not the norm.

Finally, the most important challenge is ensuring such interventions reach the many people at high risk in developing countries who currently receive little or no preventive care. Compared with developed countries many times more lives could be saved, mostly among middle aged people, if combination medications were made affordable and accessible. It would clearly have major equity implications if the decades of research in developed countries showing how to control cardiovascular disease were not translated into practicable solutions for developing countries, which are now facing an epidemic of cardiovascular disease.[8] Cost will be the key. The strategy requires many fewer measurements, and the pill need not be expensive—off patent components could cost very little.[5] It is more cost effective than threshold based strategies (for example, the treatment of hypertension)[5 10] and, combined with population wide initiatives such as reduced salt in manufactured foods, could halve population levels of cardiovascular disease.[5]

So is Wald and Law's bold claim justified? Quite possibly. Only large reductions in smoking or a few other leading health risks could achieve so much health gain.[11] Realising this enormous potential should be a major goal especially for developing countries.

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Managing chronic pain in children and adolescents

We need to address the embarrassing lack of data for this common problem

Recent epidemiological data have made nonsense of the prejudice that chronic pain is a uniquely adult problem. Chronic and recurrent pain in children and adolescents is now known to have a point prevalence of at least 15%.[1] Girls report more pain than boys, and the incidence peaks at an average age of 14 years. The most common complaint is headache, followed by recurrent abdominal pain and musculoskeletal pain.[2]

Many of the children and adolescents with chronic and recurrent pain will be managed effectively by the family doctor or may simply never come to professional attention. However, a noteworthy number of children and their families are severely affected by pain. Doctors concerned about missing a serious underlying disease invest time and energy in investigating the child and referring to specialists for further evaluation. During the time spent in this "diagnostic vacuum," the child often receives little appropriate pain management. If, as is usually the case, no specific cause can be found the child, family, and doctor often become frustrated, sometimes antagonistic towards each other, and the management of the pain goes wanting. It is this time spent in the search for meaning and cure that is thought to be crucial to how the patient and family adjust to pain. Fear and frustration are often fuelled by unhelpful or inaccurate diagnoses such as "functional" or "psychosomatic" pain. Families often interpret these labels as blaming them for the child's pain, and the labels tend to reinforce

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