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A polypill is the solution to the pharmacological management of cardiovascular risk

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'A meta-analysis is like a sausage, only God and the butcher know what goes in it and neither would ever eat any'
—Dr Franz Messerli (St Luke's-Roosevelt Hospital Center, New York City)

When the phone call came through to ask if I would put the case against the polypill I was at Lake Karapiro watching the national school rowing regatta. By odd coincidence so was Raina, my fellow debater. We discussed and foolishly I agreed. As I began to muse on the finer points of the clinical pharmacological nightmare that is the polypill, another more worrying aspect dawned on me. There I was watching this amazing group of young people, supremely fit, perfect physiques, focussed and brimming with competitive enthusiasm. I had watched them train hard several times weekly, eating incredibly healthy food, no alcohol, no smoking. How could it be that in less than four decades under the polypill concept we would be re-defining them ALL as being of sufficiently high cardiovascular risk to convince them to down a cocktail of five or six potent and potentially damaging medicines together with a large dose of unnecessary anxiety?

My mind raced over the evidence I could recall; no evidence of benefit of statins for women or primary prevention in the elderly;[1] new meta-analysis questioning use of aspirin in primary prevention;[2] huge numbers needed to treat, to harm, to medicalise; multiple interactions (90% for six drugs in the elderly); individual genetic drug metabolism; multiple contraindications; comorbidities: asthma, gout, diabetes, multiple and mixed-up side effects; an excuse to avoid healthy lifestyle choices... Surely this would be polypharmaceuticalisation on a grand and previously undreamed of scale?

Unfortunately, any debate on the relative benefits and harms of the polypill is beset by definitions. The original 2003 concept proposed by Wald and Law of several medicines for the treatment of all aged over 55 without testing has widened.[3] The same authors (who incidentally are reported as having filed a patent and a trademark application for the word 'polypill') have very recently been in

print proposing (just) three low-dose antihypertensives for all over 55, irrespective of BP. Indeed they suggest it may not be useful even to measure it.

'Our results indicate the importance of lowering blood pressure in *everyone over a certain age*, rather than measuring it in everyone and treating it in some.'[4]

Others have proposed targeted use of a polypill only for secondary prevention. Currently a half-way house using a modified polypill with the beta-blocker replaced with thiazide diuretic is being tested in NZ as primary prevention on a high-risk population.

So what are the practical difficulties of using fixed combination pills in secondary prevention, where admittedly evidence of efficacy of some of the ingredients is relatively strong? The practical problems of commencing several medicines at fixed doses to those with existing organ damage and who often have additional co-morbidities lie both in knowing which of six drugs commenced simultaneously is causing a side effect and in the inherent impossibility of individually titrating the doses of the very different ingredients. There must be a real risk of under-treatment in this very high-risk group. As an example, evidence for reduction in absolute risk (life prolongation) in those with cardiovascular disease, diabetes and heart failure is with high doses of ACE inhibitor, even if surrogate outcomes like blood pressure are used to guide treatment, what should the prescriber do if the relatively low doses in the polypill do not reduce BP to target? Is the prescriber to add another agent, or to top up the dose of one of the existing ingredients? The polypill proponents suggest a range of strength polypills as a way round this. Unfortunately, increasing the dose of say the ACE inhibitor involves doubling the dose of the statin and vice versa. I would predict that any compliance advantage for secondary prevention would quickly be lost with the need for additional pills. Alternatively, having several variations of polypill would seem to defeat the purpose. For a detailed discussion of the pharmacological problems associated with the one size fits all polypharmacy concept, I recommend an excellent critique by David Spence from London, Ontario who, in steadfastly defending the need to individualise treatment, summarises the polypill approach beautifully:

'A single pill that will succeed in all patients is not only practically, but conceptually, an inappropriate approach for the prevention of cardiovascular disease.'[5]

Returning to the original concept proposed by Wald and Law, i.e. treatment for all over a certain age without testing, the evidence of benefit to harm is likely to be unfavourable for most. This raises very significant ethical issues of whole population disease mongering. We urgently need to debate setting limits around the intrusion of population-focussed cost-effectiveness calculations into the daily lives of the healthy middle-aged and elderly population.

The polypill is a natural extension of the current obsession with absolute risk, which, in its guideline and soon to be performance indicator form, takes no consideration of the normal processes of ageing

In my view, the polypill is a natural extension of the current obsession with absolute risk, which, in its guideline and soon to be performance indicator form, takes no consideration of the normal processes of ageing. Indeed, with the original polypill proposal, the overriding risk associated with proximity to end of life (i.e. middle age) alone qualifies everyone for polypharmacy and apparently obviates the need to measure other known associated risk factors. The numbers of healthy 55-year-olds who would need to be treated each year to prevent one event runs into hundreds (if not thousands for women), and then only if one assumes that in the real life situation compliance would approximate to that in clinical trials (it doesn't), that reducing risk factors with drugs always equated to reduction in events (it doesn't) and that the Framingham dataset didn't seriously overestimate risk in the more affluent elderly—the group most likely to take such a pill (it does).

On the harms side, each and every one of those coerced into taking the cocktail will now consider themselves to have a serious medical problem. Each will run the risk of harm from the powerful drugs contained in the pill, none of which, even the aspirin, is necessarily a safe or sensible option for primary prevention.[2] Where would informed patient choice based on realistic benefits and harms fit into the mix? Early prepolyhype is not encouraging, with relative risk headlines of 80% reductions in heart disease the norm. Where are the press reports of absolute risk reduction, numbers needed to treat and to harm? Imagine the television advertisements in New Zealand and the (now redefined) patient demand they would generate?

unwittingly and without consent be changing the cause of death for those over 70.[7]

Whether a fixed combination polypill has a place as a simple and cheap intervention for specific, very high risk groups remains to be demonstrated. I will reserve judgment on the results of the current and subsequent longer trials. For some of those trialists who stick with the pill it is almost certain it will lead to a reduction of the measurement of some risk factors. Whether those reductions are sustained and result over subsequent years in clinically significant additional reduction of cardiovascular events will, I predict, depend more upon lifestyle factors beyond any beneficial physiological effects of the individual ingredients.

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In contrast to the pill for all approach, the following Christmas edition of the *BMJ*, carried a paper promoting a 'polymeal' containing fruits and vegetables, almonds, chocolate, wine, fish, and garlic.[6] Using similar theoretical statistical manipulation, the calculated reduction in cardiovascular risk (75%) was said to be as good (a guess) as that proposed by the drug cocktail and considerably safer and tastier. Exercise and abstinence from smoking similarly have major roles to play in delaying heart disease; there must be a danger that a panacea polypill will be seen as an alternative to difficult choices—'eat drink and be merry for tomorrow we have the polypill' perhaps?

In summary, my prediction is that the polypill as a secondary prevention tool will not catch on as the problems of individualisation will undermine its attractiveness. Promoting the polypill for general use in primary prevention, thereby needlessly medicalising thousands of individuals on course for a normal life expectancy, would in my view be unethical. Worse, in so doing we may

As one of my clinical pharmacology colleagues (another polypill sceptic) observed: Putting SSRIs or chemotherapy in the drinking water will help some people with depression/cancer—that doesn't mean it is the right or safe thing to do![8]

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