

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

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YES

Cardiovascular (CV) disease is the leading cause of hospitalisation and premature death in New Zealand (NZ). The difference in life expectancy between Maori and Europeans in NZ is approximately eight years, primarily due to CV disease. Current NZ Guidelines recommend lifestyle interventions (diet, physical activity, weight management and smoking cessation) plus medication therapy to address all modifiable risk factors for people with a five-year CV risk over 15% and for those with existing CV disease.

Blood pressure and cholesterol lowering medications will lower CV risk independent of age and sex, with similar relative risk reductions in people with average as well as above average blood pressure and cholesterol levels. These benefits have been demonstrated in several large-scale trials, such as PROGRESS¹ and the Heart Protection Study.² Antiplatelet therapy has also been shown to reduce CV events in high-risk patient groups.³ Thus, there is strong randomised trial

evidence that people with established cardiovascular disease or who are otherwise at high CV risk would benefit from these medications.^{1,2} Each medication works independently of the others so the benefits are cumulative.^{1,2,4}

Absolute risk of having a cardiovascular event can be halved by taking 'triple therapy': regular low-dose aspirin, lipid lowering medication, such as a statin, and blood pressure lowering medication, as recommended by the current guidelines. To reach blood pressure targets it is often more effective, and with fewer side effects, if two or more blood pressure agents are used at low doses, instead of one agent at high dose. The absolute risk of CV benefit of 'triple therapy' clearly outweighs the absolute risk of serious harm in those with a high CV risk (Figure).^{1-3,5}

However, in a recent audit of primary care PRE-DICT data, 90% of people at greater than 15% CV risk and 50% of those with existing CV disease, were not on 'triple therapy' (personal communication, Sue Wells). One of the reasons the rate is low is that it takes time, and usually several consultations, to start people on multiple medica-



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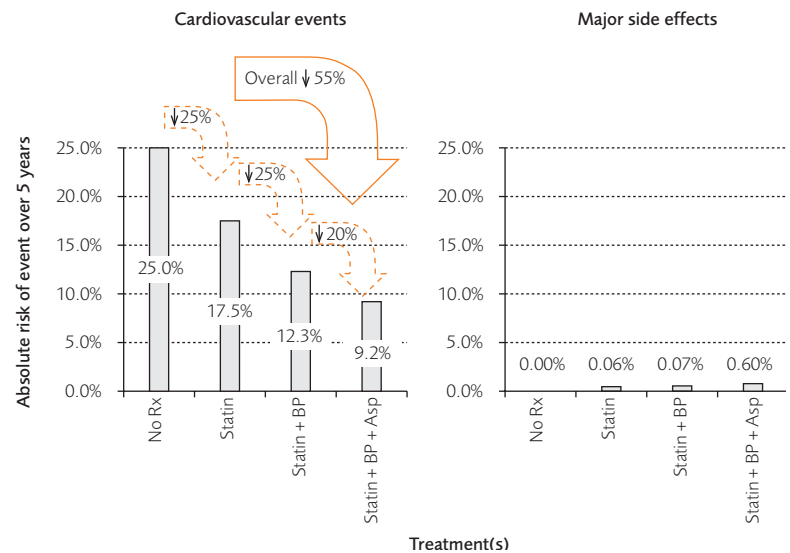
While evidence can help inform best practice, it needs to be placed in context. There may be no evidence available or applicable for a specific patient with his or her own set of conditions, capabilities, beliefs, expectations and social circumstances. There are areas of uncertainty, ethics and aspects of care for which there is no one right answer. General practice is an art as well as a science. Quality of care also lies with the nature of the clinical relationship, with communication and with truly informed decision-making. The **BACK TO BACK** section stimulates debate, with two professionals presenting their opposing views regarding a clinical, ethical or political issue.

tions. It is also difficult for people who may not have any symptoms to accept multiple medications. Cost of multiple medications is another barrier. A report by the World Health Organization (WHO) stated that 'adherence to long-term therapy for chronic illnesses in developed countries averages 50%. In developing countries, the rates are even lower.'⁶ Another systematic review found that the people who are prescribed long-term medications typically take less than half the prescribed doses.⁷ Few interventions have been found to improve adherence.⁷ Therefore, the WHO asserts that 'increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments.'⁶

A polypill has been developed to improve adherence and lower medication cost by combining four CV medications into one capsule. The polypill to be used as 'a proof of concept' in NZ will contain 75mg aspirin, 10mg lisinopril, either 40mg or 20mg simvastatin and either 12.5mg chlorohydrothiazide or 50mg atenolol. The one capsule should reduce difficulties in starting multiple medications (both for physician and for patient) and lower cost (all ingredients are 'off-patent' so have minimal cost making it available at \$30–40 per year, producing substantial savings for the government and only incurring one script fee instead of four for the patient). This also means that the polypill is very unpopular with most pharmaceutical companies.

There are concerns about the tolerability of commencing four CV medications at once compared with starting them one at a time. However, a recent nine-arm double-blind randomised controlled trial of a 'poly-cap' containing all five CV medication components compared with each of the components alone or in combinations of two or three was conducted to address this issue.⁸ The trial found that the poly-cap achieved the greatest overall benefit in terms of combined blood pressure and low density lipoprotein lowering with no significant difference in tolerability over three months. Independently-funded trials of the polypill in high CV risk populations are planned in six countries around the world, including one in NZ funded by the Health Research Council, to assess the effect and side-effect profiles com-

Figure 1. Absolute risk of cardiovascular events and fatal or life-threatening side effects with cardiovascular medications in a person with previous CVD



pared with usual care over 12 months. However, as the individual 'ingredients' of the polypill are currently used in practice anyway, one would not expect 'new' or increased rates of side effects.

Wald and Law suggested that more than 80% of CV disease could be prevented if all those over 55 years took a polypill with CV preventative medications.⁴ Unfortunately this claim has polarised opinions on the polypill, and we have neglected the 'low hanging fruit', i.e. closing treatment gaps in people with established CV disease.

If the initial prototype polypill improves adherence, and hence health outcomes in those at risk, many other varieties of polypill are likely to be developed to suit different profiles of patient and to prevent conditions that require multiple medications. For example, some have suggested having a version that contains metformin also, or replacing the atenolol with metoprolol, the more popular beta blocker in NZ. A polypill should make indicated medications easier to prescribe, easier to accept, and easier (and cheaper) to take, hence improving adherence, avoiding CV events and lowering the burden of CV disease in NZ. Thus, a polypill could be an integral part of the solution to the pharmacological management of cardiovascular risk.

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References

1. Progress Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;358:1033–1041.
2. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet* 2002;360:7–22.
3. Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86.
4. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419.
5. 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.
6. WHO. Adherence to long term therapies: evidence for action. 2003: http://www.who.int/chp/knowledge/publications/adherence_report/en/index.html.
7. Haynes RB, Yao X, Degani A, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2007.
8. The Indian Polycap Study (TIPS). Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. *Lancet* 2009.

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NO

‘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