The strong case for government funding of a polypill for the secondary prevention of cardiovascular disease in New Zealand

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ABSTRACT

Wald and Law, who popularised the term 'polypill' in 2003, proposed giving everyone above a certain age a polypill to reduce the burden of cardiovascular disease (CVD). A more compelling potential application, proposed in 2001 by the World Health Organization, is to use a polypill containing antiplatelet, statin and blood pressure-lowering therapy among people with established CVD, in whom the components are already indicated but in whom guideline implementation and adherence are suboptimal. This article outlines relevant international and New Zealand evidence on the likely benefits and harms of a polypill for the secondary prevention of CVD. The evidence indicates that the benefits are likely to outweigh the harms, particularly given the persistence of substantial treatment gaps and inequities in the management of and outcomes in CVD. The time is long overdue for the polypill to be funded for the secondary prevention of CVD.

Cardiovascular disease (CVD) is one of the major causes of mortality, morbidity and inequities globally. The World Health Organization (WHO)'s action plan to reduce the burden of CVD, as well as other non-communicable diseases, requires multi-sectoral action across the life-course.[1] Targets of the plan include improvements in behavioural risk factors (i.e. tobacco use, unhealthy diet, physical inactivity and harmful use of alcohol), biological risk factors (i.e. raised blood pressure, obesity and diabetes) and access to counselling as well as drug therapy to prevent CVD.[1] The key medications for CVD prevention are statins, blood pressure (BP)-lowering therapy and antiplatelet therapy, which are all recommended in New Zealand (NZ), as well as international guidelines, for people with established CVD.[2] Unfortunately "CVD is currently the leading pharmacologically undertreated chronic condition" in NZ.[3]

The term 'polypill' was popularised by Wald and Law in 2003, who proposed that everyone above a certain age (e.g. 55 years) should use a polypill containing aspirin, statin, three BP -lowering drugs and folic acid to reduce their risk of CVD.[4] While this remains the most well-known polypill-based cardiovascular prevention strategy, the use of the polypill appears to have been first proposed in 2001, during a WHO meeting to discuss strategies for the secondary prevention of non-communicable diseases.[5] One of ten recommendations arising from that meeting was the development of a daily fixed-dose combination pill (or polypill)

containing aspirin, statin and BP-lowering therapy for people with established CVD to address treatment gaps (suboptimal implementation of guidelines and poor patient adherence).[5] Despite the generation of a significant volume of research in the nearly 20 years since that WHO meeting, much of it from NZ, the polypill is not yet funded for use in NZ. In this article, we consider the arguments raised against polypill-based care for the secondary prevention of CVD that may explain the lack of progress, and present evidence from local and international polypill and CVD research to counter these arguments.

Doubts about the burden of future CVD among people with established CVD

CVD (including diabetes) accounted for 17% of all health loss in the total NZ population in 2013.[6] In an analysis of data from people who had their first CVD risk assessment between 2002 and 2007, among those with prior CVD the absolute risk of a further CVD event was much higher (approximately 20%) than the risk of a first CVD event among those without established CVD.[7] The study also found that almost half of the CVD events during follow up occurred among those with prior CVD and concluded that patients with prior CVD should be afforded the highest priority for intensive preventive management in primary care.[7]

Doubts about the presence of CVD treatment gaps among people with established CVD

According to the NZ Health Quality and Safety Commission's Atlas of Healthcare Variation, consistent dispensing of triple therapy (antiplatelet/anticoagulant, BP-lowering and lipid-lowering therapy) among people with a history of atherosclerotic CVD was 59% in 2011, ranging from 54% among Māori to 63% among Indian people.[8] There does not appear to have been an improvement in access or equity of access since that time: an unpublished analysis of people who had their first CVD risk assessment in Auckland and Northland between 2012 and 2016 showed that 57% of those with the same history of atherosclerotic disease were dispensed triple therapy in the year following their CVD risk assessment, ranging from 54% among Māori to 72% among Indian people. (V Selak, Personal communication). This treatment gap is evident internationally. A survey published in 2011 found only 44% of people with a prior CVD event in high-income countries reported taking at least three of four recommended preventive medications (aspirin, statin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and another BP-lowering drug).[9]

Concerns about the potential effect of polypills on ethnic inequities in CVD

Interventions that are shown to be effective in trials do not necessarily reduce ethnic disparities, and may in fact widen them.[10 11] The IMProving Adherence using Combination Therapy (IMPACT) trial (n=513, 50% Māori), conducted in the Auckland and Waikato regions between 2010 and 2013[12], found that participants in the polypill arm had higher adherence to combination therapy than those in the usual care arm (81% vs. 46%, RR 1.75, 95% CI 1.52 to 2.03) and there was no heterogeneity in this treatment effect by history of CVD at baseline.[13] Polypill-based care was associated with an increase in the use of recommended medications among Māori (RR 1.87, 95% CI 1.50–2.34) and non-Māori (RR 1.66, 95% CI 1.37–2.00) when compared with usual care at 12 months, and there was no statistically significant heterogeneity in this outcome by ethnicity.[14] Given baseline absolute differences in the use of recommended medications and the consistency of the proportional effect of this intervention by ethnicity, polypill-based care is likely to reduce absolute inequities between Māori and non-Māori in the use of recommended cardiovascular preventative medications[14] and presents an important potential means of reducing inequities in CVD.

Doubts about the effectiveness of polypills

An individual participant data meta-analysis compared polypill-based care with usual care in 3140 patients with CVD or at high risk across six countries (comprising the Single Pill to Avert Cardiovascular Events [SPACE] Collaboration, and including the IMPACT trial).[15] The comparator for the SPACE trials was usual care because an inactive comparator would have been

unethical given that all participants had indications for cardiovascular preventive medication, and the trials were unblinded because it would have been impossible to mask whether treatment was received as a single or multiple tablets. In the meta-analysis participants in the polypill arm had higher adherence to combination therapy (80% vs. 50%, risk ratio, RR, 1.58, 95% CI 1.32 to 1.90), lower systolic BP (-2.5 mmHg, 95% CI -4.5 to -0.4) and lower low density lipoprotein (LDL) cholesterol (-0.1 mmol/L, 95% CI -0.2 to 0.0).[15] The apparent discrepancy between a large improvement in adherence and modest improvements in risk factor levels is likely to be because of atypically high treatment rates in the usual care arm (at baseline 85% and 90% of patients were already using statin and BP-lowering therapy, respectively), the composite nature of the adherence outcome, and, in the case of cholesterol, because more potent statins were available for use in the usual care arm than was contained in the available polypills (simvastatin 40mg). Treatment effects were consistent whether or not participants had established CVD at baseline.[15] Baseline treatment levels were a major effect modifier for adherence and systolic BP with greatest improvements seen among those under-treated at baseline.[15] In a separate analysis, those randomised to polypill-based care were found to be more likely than those receiving usual care to achieve European Society for Cardiology targets for BP (62% vs 58%, RR 1.08, 95% CI 1.02 to 1.15), LDL cholesterol (39% vs 34%, RR 1.13, 95% CI 1.02 to 1.25) and all three targets for BP, LDL and adherence to antiplatelet therapy (the latter only applicable to those with a prior CVD event) simultaneously (24% vs 19%, RR 1.27, 95% CI 1.10 to 1.47) at 12 months.[16] There was no difference between groups in antiplatelet adherence as it was already high (96% vs 96%, RR 1.00, 95% CI 0.98 to 1.01).[9]

Doubts about the cost-effectiveness of polypills

In a within-trial cost analysis of polypill-based care versus usual care with separate medications in Australia, there was a statistically significantly lower mean pharmaceutical expenditure of $AU989 (95% CI $648-$1331) per patient per year in the polypill arm compared with usual care (adjusted, excluding polypill cost as it was not marketed in Australia at the time of the trial).[17] A within-trial cost-effectiveness study among people with established CVD in India found the incremental cost-effectiveness ratios for polypill-based care compared with usual care ranged between cost saving to US$75 per 10% increase in adherence for a polypill price of US$0.94/day.[18] Further, improvements in risk factor control are likely to lead to reduced health care costs through health improvements.

Concerns about the safety of polypills and their potential negative impact on lifestyle interventions

A 2018 review of the safety of polypills for the secondary prevention of CVD, based on evidence from relevant trials, found no evidence that use of individual component medications within a combination medication was any less safe than individual component medications.[19] An individual participant meta-analysis of data from the SPACE trials found no difference in lifestyle risk factors in those randomised to polypill-based care compared with usual care over a median of 15 months, either across all participants combined, or in a range of subgroups.[20]

Concerns about the acceptability of polypills for patients and doctors

Polypill-based care has been found to be generally acceptable to trial participants and their physicians.[21] The medications in the polypill have been in use for decades and are already recommended for use simultaneously: as noted previously, NZ's 2018 CVD risk assessment and management guidelines, consistent with major international guidelines, recommend statins, BP-lowering therapy and antiplatelet therapy for people with established CVD. Most GPs who prescribed the polypill during the IMPACT trial found polypill-based care satisfactory or very satisfactory for starting treatment (91%), BP control (82%), cholesterol control (78%), tolerability (81%), and prescribing according to NZ guidelines (84%).[13] The most commonly reported advantage of polypill-based care among the GPs was improved adherence (57%), while lack of flexibility was cited as the most important disadvantage (37%). Importantly, 90% of the GPs reported that if they had another patient like

their patient on the IMPACT trial they would start them on a polypill if it were available.

Polypills may not contain the right components or the right ratio of doses for any given person. This is a limitation of any polypill-based approach which cannot be seen as a panacea. For this reason, patients were only included in the IMPACT trial if their GP confirmed that: all medications in an available polypill were indicated; there was no contraindication to any of the components of the relevant polypill; and the patient would not be better managed by receiving the medications separately.[12] Further, GPs were able to add any additional medication as required, as well as discontinue the polypill if for any reason it wasn't suitable for their patient.[12]

Doubts that polypills have regulatory approval

Initial technical challenges of developing stable and bioequivalent polypills have now been met. Trinomia, a polypill containing aspirin 100mg, atorvastatin 20mg and ramipril 2.5-10mg, was approved for use in the secondary prevention of CVD in NZ by Medsafe in 2017. However, it has not yet been funded by PHARMAC. An application to PHARMAC for funding of Trinomia was made in 2017. The Cardiovascular Subcommittee of PHARMAC's Pharmacology and Therapeutics Advisory Committee (PTAC) recommended that such polypills be funded,[22] but PTAC did not accept their recommendation on the basis that "applications for fixed-dose combination pills should only be considered if they provided evidence regarding clinical outcomes rather than surrogate outcome measures".[23]

Concerns about the lack of polypill outcome trials

The preferred endpoint for a clinical trial assessing effectiveness is generally an outcome that is relevant to patients, such as CVD events, as opposed to surrogate or intermediate markers such BP or cholesterol. We consider that outcome trials are not needed in the case of a polypill for the secondary prevention of CVD. NZ's 2018 CVD risk assessment and management guidelines, consistent with major international guidelines, already recommend statins, BP-lowering therapy and antiplatelet therapy, simultaneously, for people with established CVD because of the strength of evidence supporting the use of these treatments in this group and their independent effects on the risk of CVD.[2] As noted by some members of the Cardiovascular Subcommittee of PTAC, "surrogate markers have been accepted as sufficient to fund other cardiovascular medications, eg ezetimibe" and there are "a number of funded combination products in the diabetes, HIV, and respiratory therapeutic groups for which additional trials demonstrating clinical outcomes over and above the individual agents had not been necessary".[24] Outcome trials are very expensive to run and there has been little interest among pharmaceutical companies in funding the formulation of a polypill comprising generic component medications,[21] let alone funding outcome trials for these products. Further, the heretofore lack of outcome trials needs to be considered alongside all available evidence, as outlined above. This evidence supports polypill-based care for those with existing CVD on the basis of (1) effectiveness, (2) safety, (3) cost-effectiveness and (4) equity.

Nevertheless, a polypill outcome trial has now been completed and its results just published. The PolyIran cluster randomised trial compared a polypill (containing aspirin, atorvastatin, hydrochlorothiazide and either enalapril or valsartan) with non-pharmacological preventive interventions alone. A total of 6838 people aged 50 years or older were enrolled between 2011 and 2013, and followed up for 5 years.[25] The trial found a 34% reduction in major cardiovascular events in the polypill compared with the control group (hazard ratio, HR, 0.66, 95% CI 0.55-0.80), and a statistically significant effect was observed in the subgroup of patients with established CVD at baseline (HR 0.61, 95% CI 0.49-0.75).

Potential use cases for a polypill in the secondary prevention of CVD

The evidence indicates that the benefits of a polypill for the secondary prevention of CVD are likely to outweigh the harms, particularly given the persistence of substantial treatment gaps and inequities in the management of and outcomes in CVD. However, polypill-based care should not be seen as a panacea. The use of a polypill would be challenging during a period when frequent medication changes are needed,

such as is typically the case during the acute phase following a cardiovascular event. To our knowledge no polypill has yet been developed that contains high intensity statin therapy (e.g. atorvastatin 80mg), as is recommended for ST-elevation myocardial infarction by NZ 2013 management guidelines.[26] For these reasons polypill-based care is most suited to those with stable, non-acute CVD. Two specific use-cases have been proposed in a recent publication by Webster et al that we endorse:

1. Established indications for all polypill components in patients taking the drugs already as separate pills ('established indications, straight substitution')

2. Established indications for all polypill components in patients not taking them all due to barriers in uptake and/or adherence ('established indications, step-up substitution').[27]

Comprehensive action to address the burden of CVD

While this article has focused on a polypill containing antiplatelet, statin and BP-lowering therapy, there are other strategies that could also be used to address the pharmacological under-treatment of CVD in NZ. These strategies include: (1) a polypill containing a statin and BP-lowering drug without an antiplatelet (as is currently available in Australia), (2) over-the-counter statins at pharmacies (as is currently available in the United Kingdom), (3) six-month prescriptions for CVD pharmacotherapy (as is currently available for oral contraceptives in NZ), and (4) improved health literacy and information for decision-making.[3] None of these strategies are mutually exclusive of one another. Further, pharmacotherapy-based approaches are just one aspect of action needed to address the burden of CVD. In order to substantively and sustainably reduce the burden of CVD, multi-sectoral action is required across the life-course that supports improvements in behavioural risk factors, biological risk factors and access to counselling, as well as drug therapy.

Conclusion

The evidence in support of polypill-based care as an option for the secondary prevention of CVD is substantial and the time is long overdue for polypills to be funded for this indication, particularly given their potential as a means of reducing inequities in CVD.

Competing interests:
Nil.

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