Role of polypills in primary prevention of CVD

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Cardiovascular polypills containing aspirin, blood pressure lowering-medication and statins have been shown to improve adherence to recommended medications in patients at high risk of cardiovascular disease. However, the balance of risks and benefits of using polypills for primary prevention of cardiovascular disease is unclear. This is likely to be further clarified shortly with several large scale, long-term randomised trials underway.

Cardiovascular diseases (CVDs) remain a leading cause of premature death and disability in Australia. A number of effective preventive medications such as blood pressure-lowering drugs, statins and antiplatelet agents are available.[1] These are generally recommended for individuals with established CVD or otherwise at high risk of a CVD event, although optimal use of such medications has consistently been shown in only about one-half of this population in contemporary Australian practice.[2-4] Over recent years, broad use of cardiovascular 'polypills' has been advocated to reduce the population burden of CVD.

What are cardiovascular 'polypills'?

The concept of combining multiple classes of drugs into a single pill to improve accessibility and adherence to preventive therapy for CVD has a long history. The term 'asp-olol' was coined for a combination of aspirin and atenolol in the 1970s and patents claiming rights over combinations of various cardiovascular drugs have been filed since the late 1990s.[5-7] The World Health Organization and The Wellcome Trust convened a meeting in 2001 to discuss evidence-based and affordable interventions for non-communicable diseases.[8] A major impetus for the meeting was the potential for fixed-dose combinations containing aspirin, antihypertensives and statins to encourage adherence and reduce the costs of treatment.

The term 'polypill' was introduced in 2003 when it was suggested that the use of a single pill (containing aspirin, a statin, three

Key points

- **Cardiovascular polypills combine commonly recommended blood pressure-lowering medications and statins, with or without aspirin, for the prevention of cardiovascular disease.**
- **In the context of secondary and high-risk primary prevention, the availability of polypills has been shown to improve adherence to these recommended treatments, with corresponding lowering of blood pressure and LDL-cholesterol levels.**
- **Evidence about the risks and benefits of polypill use for the primary prevention of cardiovascular disease in a broader population is not yet available.**
- **Over the next few years, the results of at least three large studies evaluating a range of polypills for cardiovascular disease prevention will become available.**

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antihypertensives and folic acid) in every person aged over 55 years would reduce population CVD burden by more than 80%.[9] Since then, the term 'polypill' has been applied to more generally define fixed-dose combination therapy for the prevention of CVD, which includes a statin and blood pressure-lowering drugs, with or without aspirin.

Does current evidence support the use of cardiovascular 'polypills' in any population?

Ten years on from the term 'polypill' being first used, several short-term, placebo-controlled clinical trials have provided further evidence on the feasibility and efficacy of such an approach in lowering blood pressure and LDL-cholesterol levels (Table 1).[10-14] The trials have

Table 1. Polypill versus placebo trials

Study	Study population characteristics	Drugs in the polypill (daily dose)	Comparison, number of patients and duration of follow up	Results		Notes
				Observed mean difference in SBP (mmHg)	Observed control-adjusted reduction in LDL (mmol/L)	
Malekzadeh, et al. 2010[10]	Primary prevention (no previous CVD) Inclusion criteria: age >50/55 years, no previous CVD; not on active blood pressure- or lipid-lowering drugs. No exclusion for diabetes	Aspirin (81 mg), enalapril (2.5 mg), atorvastatin (20 mg), hydrochlorothiazide (12.5 mg)	Placebo n = 234 12 months	2.4	0.45	Imbalance in baseline characteristics suggests possible inadequate randomisation. Differential follow-up rate: 68% in intervention, 78% in control
PILL Collaborative Group 2011[11]	Primary prevention (no previous CVD) Inclusion criteria: five-year CVD risk >7.5% (based on Framingham risk score) or 5 to 7.5% and two CVD risk factors. No exclusion for diabetes	Aspirin (75 mg), lisinopril (10 mg), hydrochlorothiazide (12.5 mg), simvastatin (20 mg)	Placebo n = 189 12 weeks	9.9	0.75	99% follow up
Wald, et al. 2012[12]	Primary prevention (no previous CVD) Inclusion criteria: over 50 years of age	Amlodipine (2.5 mg), losartan (25 mg), hydrochlorothiazide (12.5 mg), simvastatin (40 mg)	Placebo n = 86 12 weeks (cross-over randomised controlled trial)	17.9	1.4	98% follow up
Indian Polycap Study (TIPS) 2009[13]	Primary prevention (no previous CVD) Inclusion criteria: at least one cardiovascular risk factor (including diabetes)	Hydrochlorothiazide (12.5 mg), atenolol (50 mg), ramipril (5 mg), simvastatin (20 mg), aspirin (100 mg)	Multi-armed study with arms not taking various classes of medication used as comparator n = 2053 8 to 12 weeks (multi-armed study)	7.4	0.72	85% follow up

Abbreviations: CVD = cardiovascular disease; LDL = low-density lipoprotein; SBP = systolic blood pressure.
Adapted from Elley CR, et al. PLoS ONE 2012; 7: e52145-e.[14]

largely shown polypills will reduce systolic blood pressure and LDL-cholesterol levels to the degree expected from the drugs and dosages used, allowing for observed rates of adherence. In addition, several large-scale trials of polypill-based therapy compared with usual care in high-risk patients (a combination of secondary prevention and high-risk primary prevention) have demonstrated expected benefits on adherence with corresponding improvements in systolic blood pressure and LDL-cholesterol level.[15-17] Results from the Use of a Multidrug Pill in Reducing Cardiovascular Events (UMPIRE) trial are shown in Table 2.[15] The results are consistent with those in meta-analyses (unpublished data) combining the UMPIRE trial with two other similar studies (Kanyini Guidelines Adherence with the Polypill [Kanyini-GAP] study[16] and Improving Adherence using Combination Therapy [IMPACT] study).[17] The polypill used in these trials included aspirin, simvastatin, lisinopril and atenolol or hydrochlorothiazide.

The potential use of a polypill in secondary prevention is much less controversial as all major guidelines recommend multidrug therapy with blood pressure lowering, statins and antiplatelets in such patients. However, there is still much debate over the role of a polypill for primary prevention in a broader group, partly due to the uncertain risk:benefit ratio for the use of aspirin in people without established CVD.[18]

Primary prevention in patients at low-moderate CVD risk

Some advocates for polypill use in people without established CVD argue that widespread use of a polypill (combined with other population-based strategies) with minimal screening, such as age alone (≥55 years) or age plus one additional risk factor, could prevent the majority of CVD events in both high- and low-income countries.[19] However, there are currently no data on the long-term safety and clinical benefits of using a polypill in this context.

Three large-scale, placebo-controlled clinical trials are currently underway to address the outstanding questions about the use of a polypill in low-moderate risk primary prevention. These trials are:

- Prevention of Cardiovascular Disease in Middle-aged and Elderly Iranians Using a Single PolyPill (PolyIran) study[20]
- Heart Outcomes Prevention Evaluation-3 (HOPE-3)[21]
- The International Polycap Study 3 (TIPS-3).[22]

These trials are studying the primary prevention of CVD events in patients at moderate risk who have neither a current indication for or against preventive medications, based on current clinical guidelines. Due to the concern over the risk:benefit ratio of aspirin in this context, the HOPE-3 trial has not included aspirin in its design; however, aspirin is included in the polypill used in PolyIran study and is included in one of the factorial arms of TIPS-3. Results from these studies are expected from late 2015.

Primary prevention in patients at high CVD risk

Current Australian guidelines recommend the use of statins and blood pressure-lowering medications in patients with a calculated absolute risk of more than 15% over five years regardless of baseline blood pressure or LDL-cholesterol levels.[23] Use of fixed-dose combination therapy containing a statin and blood pressure-lowering medications would be expected to have net benefits in this population.

The Kanyini-GAP study was a randomised trial investigating polypill-based therapy versus usual care involving 623 patients either with established CVD or at high calculated risk from Australian general practices. In the subgroup of patients in primary prevention, polypill-based care was associated with a significant improvement in adherence to recommended CVD preventive therapy (relative risk, 2.17; 95% confidence interval, 1.62 to 2.90).[16] This was due to a combination of an increased prescription of recommended therapy by general practitioners as well as improved patient adherence to prescribed therapy. The polypills used in the Kanyini-GAP study did contain aspirin in line with guidelines at the time; however, currently the balance of risks and benefits with aspirin use in this population is also considered uncertain.

Table 2. Effect of polypill-based therapy on adherence, systolic blood pressure and LDL-cholesterol level (UMPIRE study)[15]

	Polypill group (n = 1002)	Usual care (n = 1002)	Treatment effect* (95% confidence interval)	P value
Adherence†	829/961 (86%)	621/960 (65%)	RR = 1.31 (1.26 to 1.41)	<0.001
Systolic blood pressure, mmHg	129.2 (128.1 to 130.2)	131.7 (130.7 to 132.8)	-2.6 (-4.0 to -1.1)	<0.001
LDL-cholesterol level, mmol/L	2.18 (2.14 to 2.22)	2.29 (2.25 to 2.33)	-0.1 (-0.17 to -0.05)	<0.001

Adapted from Thom S, et al. JAMA 2013; 310: 918-929.[15]

* Treatment effect: relative risk (RR) for adherence and mean difference for blood pressure and cholesterol measures.

† Self-reported use of antiplatelet, statin and two or more blood pressure-lowering drugs.

Availability of polypills on the market

Despite the mounting evidence for effectiveness for polypills in improving adherence to recommended therapy, very few of these polypills are on the market, especially in high-income countries such as Australia. One polypill containing aspirin, simvastatin and varying doses of ramipril has recently obtained marketing approval in Latin America and several European countries. Several polypills containing aspirin, statin and multiple blood pressure-lowering medications are available in India.

In Australia, a fixed-dose combination of amlodipine besylate and atorvastatin calcium has been available for some time, with a current prescription rate of over one million per year.[24] It should be noted, however, that PBS listing permits use of this fixed-dose combination only in patients for whom a statin is indicated and who also have hypertension or angina. This precludes use in patients who are at high calculated risk of CVD but without raised blood pressure.

Several public-private partnerships globally are actively working on obtaining marketing approval in high-income countries for polypills with multiple low-dose blood pressure-lowering medications (for maximal blood pressure-lowering effect with reduced side effects) and statins, both with and without aspirin. Potential polypills are likely to include a range of dual and triple blood pressure-lowering combinations and a range of doses to reduce concerns about the inability to titrate individual drugs when using fixed-dose combination therapy.

Conclusion

Cardiovascular polypills containing blood pressure-lowering medication and statins have been shown to improve adherence to recommended medications in patients at high risk of CVD, both in the primary and secondary prevention context. The long-term balance of risks and benefits of using such polypills (with and without aspirin) for primary prevention in patients at low-moderate risk of CVD is unclear; however, several large-scale, long-term randomised trials are currently underway with results expected over the next one to five years. **CT**

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2013; 380: 2095-2128.
2. Webster RJ, Heeley EL, Peiris DP, Bayram C, Cass A, Patel AA. Gaps in cardiovascular disease risk management in Australian general practice. Med J Aust 2009; 191: 324-329.
3. Heeley EL, Peiris DP, Patel AA, et al. Cardiovascular risk perception and evidence--practice gaps in Australian general practice (the AusHEART study). Med J Aust 2010; 19: 254-259.
4. Peiris DP, Patel AA, Cass A, et al. Cardiovascular disease risk management for Aboriginal and Torres Strait Islander peoples in primary health care settings: findings from the Kanyini Audit. Med J Aust 2009; 191: 304-309.
5. Liang MH, Manson JE, inventors. Treatment of patients at elevated cardiovascular risk with a combination of a cholesterol-lowering agent, an inhibitor of the renin angiotensin system, and aspirin. United States patent No 6,576,256 B2. 2003.
6. Tobert JA, Merck & Co Inc, inventors. Combination therapy for reducing the risks associated with cardiovascular disease. WO 1997038694 A1. 1997.
7. Wald NJ, Law MR, inventors; Pharmaceutical formulation for the prevention of cardiovascular disease patent GB 2361 185 A.
8. World Health Organization. Secondary prevention of non communicable disease in low and middle income countries through community-based and health service interventions. Geneva: WHO; 2002.
9. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003; 326: 1419.
10. Malekzadeh F, Marshall T, Pourshams A, et al. A pilot double-blind randomised placebo-controlled trial of the effects of fixed-dose combination therapy ('polypill') on cardiovascular risk factors. Int J Clin Pract 2010; 64: 1220-1227.
11. Rodgers A, Patel A, Berwanger O, et al; Pill Collaborative Group, An international randomised placebo-controlled trial of a four-component combination pill ("polypill") in people with raised cardiovascular risk. PloS ONE 2011; 6: e19857.
12. Wald DS, Morris JK, Wald NJ. Randomized polypill crossover trial in people aged 50 and over. PLoS ONE 2012; 7: e41297.
13. Yusuf S, Pais P, Afzal R, et al. 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; 373: 1341-1351.
14. Elley CR, Gupta AK, Webster R, et al. The efficacy and tolerability of 'polypills': meta-analysis of randomised controlled trials. PLoS ONE 2012; 7: e52145.
15. Thom S, Poulter N, Field J, et al. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. JAMA 2013; 310: 918-929.
16. Patel A, Cass A, Rodgers A, et al. A pragmatic trial of a polypill-based strategy to improve adherence to indicated preventive treatments among people at high cardiovascular disease risk. Eur J Prev Cardiol 2014 Mar 27 [Epub ahead of print].
17. Selak V, Elley CR, Bullen C, et al. Effect of fixed dose combination treatment on adherence and risk factor control among patients at high risk of cardiovascular disease: randomised controlled trial in primary care. BMJ 2014; 348.
18. Antithrombotic Trialists Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. The Lancet 2009; 373: 1849-1860.
19. Lonn E, Bosch J, Teo KK, Pais P, Xavier D, Yusuf S. The polypill in the prevention of cardiovascular diseases: key concepts, current status, challenges, and future directions. Circulation 2010; 122: 2078-2088.
20. Prevention of cardiovascular disease in middle-aged and elderly Iranians using a single polypill (Polyiran). NCT01271985. http://clinicaltrials.gov (accessed May 2015).
21. Heart Outcomes Prevention Evaluation-3 (HOPE-3). NCT00468923. http://clinicaltrials.gov (accessed May 2015).
22. The International Polycap Study 3 (TIPS-3). NCT01646437. http://clinicaltrials.gov (accessed May 2015).
23. National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk, Sydney: National Stroke Foundation; 2012.
24. Australian Government Department of Health. PBS Statistics. PBS expenditure and prescriptions: expenditure and prescriptions twelve months to 30 June 2012. www.pbs.gov.au.

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