ARTICLE

The 'polypill' in the prevention of cardiovascular disease

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SUMMARY

A polypill is a combination of several drugs acting on different risk factors in one formulation. The concept has been proposed as a strategy for reducing cardiovascular events.

Several trials have assessed the efficacy of the polypill compared to placebo for primary prevention. These trials showed short-term risk factor reductions, approximately equivalent to the predicted effects of the individual components. At present, the effect of the polypill on the primary prevention of cardiovascular morbidity and mortality is unknown.

Large trials have been completed comparing a polypill-based strategy with usual care in populations with established indications for the component drugs. These trials have shown improved adherence with a polypill-based strategy.

Introduction

Cardiovascular diseases are the leading cause of premature death and disability globally, despite effective strategies to prevent these conditions.[1] The concept of combining multiple classes of drugs into a single pill to improve accessibility and adherence to preventive therapy for cardiovascular disease 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.[2-4]

The first major scientific meeting on the concept of a fixed-dose combination pill for preventing cardiovascular disease was held in 2001. The World Health Organization and The Wellcome Trust convened the meeting to discuss evidence-based and affordable interventions for non-communicable diseases.[5] A major impetus for the meeting was the potential for fixed-dose combinations containing aspirin, antihypertensives and cholesterol-lowering drugs (statins) to encourage adherence and reduce the costs of treatment.

The concept of a fixed-dosed combination pill was discussed in a Lancet editorial in 2002[6] and effectiveness and cost-effectiveness analyses were published in the 2002 World Health Report.[7] The term 'polypill' was introduced in 2003[8] when it was suggested that the use of a single pill (containing aspirin, a statin, three antihypertensives and folic acid) in everyone aged over 55 years would reduce cardiovascular disease by more than 80%. The rationale for using three antihypertensive drugs, each at half dose, was to maximise the blood pressure lowering effects, while reducing the risks of adverse effects from any one class of drug.

Clinical trials

Several clinical trials have provided evidence on the feasibility and efficacy of polypills in clinical practice. The polypills used in these trials had different components, however all generally included aspirin, antihypertensives and cholesterol-lowering drugs.

These trials can be broadly grouped into two types:

- comparisons of polypill versus placebo or no treatment – in people with no indications for any of the component drugs, for example people without currently defined hypertension, dyslipidaemia or vascular disease, but who have an above average cardiovascular risk
- polypill versus usual care – in patient populations with indications for **all** the component drugs, for example patients with established coronary disease.

Such trials are crucial to establish the efficacy of cardiovascular polypills and the effectiveness of polypill-based strategies. It is necessary to show that any benefits outweigh the adverse effects of giving a polypill to many people for primary prevention. Using polypills as part of a strategy to improve the appropriate use of medication by patients with established indications for all the components has also raised theoretical concerns that the lack of flexibility associated with fixed combinations may

limit tailoring of individual medications, leading to less optimal control of risk factors. There is also concern that polypills may divert attention from appropriate lifestyle measures to prevent cardiovascular disease.

Polypill versus placebo or no treatment (Table 1)

Several short-term trials have been completed.[9-12] Three trials[10-12] found short-term reductions in risk factors. These were consistent with the expected size of effects (based on published meta-analyses of placebo-controlled trials of antihypertensives and statins) taking into account the baseline risk factors and adherence to treatment. The adverse effects and tolerability of the polypills were consistent with those expected from the individual components.

One study only showed very small risk factor reductions with the polypill compared to placebo.[9] However, imbalances in baseline risk factors suggest the possibility of a flaw in the randomisation process. This study also had low and differential follow-up rates (68% in intervention, 78% in control) so the results should be interpreted with caution.

Three large-scale placebo-controlled clinical trials are underway:

- Prevention of Cardiovascular Disease in Middle-aged and Elderly Iranians Using a Single PolyPill – PolyIran[13]
- Heart Outcomes Prevention Evaluation-3 – HOPE-3[14]
- The International Polycap Study 3 – TIPS-3.[15]

These trials are studying the primary prevention of cardiovascular disease events. The use of polypills in people with an average risk of cardiovascular disease remains contentious, because of ongoing uncertainty over the harm–benefit ratio of the drugs, particularly aspirin. Due to this concern, the HOPE-3 trial has not included aspirin in its polypill, however aspirin is included in the polypill used in the other trials.

The TIPS-3 trial has a 2 x 2 x 2 factorial design (the three components under investigation are the PolyCap, aspirin and vitamin D). It aims to provide some clarity on the harm–benefit ratio of aspirin being included in a primary prevention polypill. TIPS-3 and HOPE-3 are recruiting patients according to age and other risk factors which place them at moderate risk of a cardiovascular disease event over 5–10 years (for example men at least 55 years old with an INTERHEART risk score of at least 10, which is indicative of moderate short-term risk of experiencing a myocardial infarction).[16] The PolyIran study is restricted to people aged 50–79 years.

Polypill versus usual care (Table 2)

The first randomised trial to compare a polypill versus usual care was conducted in Sri Lanka in 216 patients without established disease, but with a 10-year cardiovascular disease risk of at least 20%.[17] This study did not show any significant improvement in adherence, systolic blood pressure or total cholesterol with the polypill. However, the authors of this open-label trial noted that the 'usual care' group received an unusually high level of care following randomisation.

The population in which there is perhaps the least controversy about the potential role of a polypill is patients with established disease, or who are at high risk of cardiovascular disease (at least 15% over five years) and have indications for antihypertensives, cholesterol-lowering and antiplatelet drugs. There are currently four trials, three of which are part of the Single Pill to Avert Cardiovascular Events (SPACE) Collaboration (www.spacecollaboration.org). This is an international group of academic researchers conducting independent, publicly funded, randomised trials. All these studies have used very similar protocols deliberately designed to maximise comparability and to facilitate a meta-analysis of individual patient data.

Initial results from two of the SPACE trials (Use of a Multidrug Pill In Reducing cardiovascular Events – UMPIRE[18] and Kanyini Guidelines Adherence with the Polypill – Kanyini-GAP[19]) have been reported. In both, the polypill-based strategy substantially improved the use of the indicated drugs. In the much larger UMPIRE study this was associated with improvements in blood pressure and cholesterol.[18] The other SPACE trial has completed patient follow-up visits and results are expected later in 2014.[20]

The planned meta-analysis of the three SPACE trials will clarify more precisely the effect of a polypill on the primary outcomes of adherence, systolic blood pressure and total cholesterol. Meta-analysis will also provide the opportunity for looking at subgroups of patients, such as women and the elderly, and primary versus secondary prevention. Results from the meta-analysis will be reported in 2014.

FOCUS is another randomised trial currently underway in Spain, Argentina, Brazil and Paraguay.[21] This trial involves an initial 4000-patient phase aimed at identifying barriers to the implementation of secondary preventive therapies following myocardial infarction. Subsequently, a 1340-patient randomised trial of a polypill versus individual therapies will assess adherence. The results of FOCUS are not expected for several years.

Table 1 **Polypill versus placebo in primary prevention trials** *

Study	Study population characteristics (no previous cardiovascular disease)	Drugs in the polypill (daily dose)	Comparison Number of patients Duration of follow-up	Results		Notes
				Observed mean difference in systolic blood pressure (mmHg)	Observed control-adjusted reduction in low density lipoprotein (mmol/L)	
Malekzadeh et al 2010[9]	Inclusion criteria: >50/55 years, no previous cardiovascular disease; 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=475 12 months	2.4	0.45	Imbalance in baseline characteristics suggests possible inadequacy of randomisation Differential follow-up rate: 68% in intervention, 78% in control
Pill Collaborative 2011[10]	Inclusion criteria: five-year cardiovascular disease risk >7.5% (based on Framingham risk score) or 5–7.5% and two cardiovascular disease risk factors. No exclusion for diabetes	aspirin (75 mg) lisinopril (10 mg) hydrochlorothiazide (12.5 mg) simvastatin (20 mg)	placebo n=378 12 weeks	9.9	0.75	99% follow-up
Wald 2012[11]	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 control trial)	17.9	1.4	98% follow-up
The Indian Polycap Study 'TIPS' 2009[12]	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 drugs used as comparator n=2053 12 weeks multi-armed study (some 8–12 weeks)	7.4	0.72	85% follow-up

* adapted from Elley, 2012[22]

Table 2 **Polypill versus usual care trials**

Study (location)	Study population characteristics	Drugs in the polypill (daily dose)	Number of patients	Duration of follow-up	Outcomes being studied	Results
Sri Lanka Polypill study[17] (Sri Lanka)	≥50 years old if female and ≥40 years old if male 10-year total cardiovascular disease risk score ≥20%	RHP Version 2b: aspirin 75 mg simvastatin 20 mg lisinopril 10 mg hydrochlorothiazide 12.5 mg	216	3 months	systolic blood pressure, total cholesterol, 10-year cardiovascular disease risk	No significant difference in systolic blood pressure, total cholesterol
UMPIRE[18] (UK, Ireland, Netherlands, India)	Established cardiovascular disease or cardiovascular disease risk of >15% over 5 years	RHP version 1c: aspirin 75 mg lisinopril 10 mg simvastatin 40 mg atenolol 50 mg RHP version 2c: aspirin 75 mg lisinopril 10 mg simvastatin 40 mg hydrochlorothiazide 12.5 mg	2004	minimum 12 months	adherence, systolic blood pressure, total cholesterol	Significant improvement in adherence, systolic blood pressure and low density lipoprotein cholesterol
Kanyini-GAP[19] (Australia)	Established cardiovascular disease or cardiovascular disease risk of >15% over 5 years	RHP version 1c: aspirin 75 mg lisinopril 10 mg simvastatin 40 mg atenolol 50 mg RHP version 2c: aspirin 75 mg lisinopril 10 mg simvastatin 40 mg hydrochlorothiazide 12.5 mg	623	minimum 12 months	adherence, systolic blood pressure, total cholesterol	Significant improvement in adherence
IMPACT[20] (New Zealand)	Established cardiovascular disease or cardiovascular disease risk of >15% over 5 years	RHP version 1c: aspirin 75 mg lisinopril 10 mg simvastatin 40 mg atenolol 50 mg RHP version 2c: aspirin 75 mg lisinopril 10 mg simvastatin 40 mg hydrochlorothiazide 12.5 mg	513	minimum 12 months	adherence, systolic blood pressure, low density lipoprotein cholesterol	2014
FOCUS[21] (Argentina, France, Italy, Spain, Switzerland)	Postmyocardial infarction	aspirin 100 mg simvastatin 40 mg ramipril (2.5, 5, 10 mg)	Phase 1 – 4000 Phase 2 – 1340	9 months	adherence, blood pressure, low density lipoprotein cholesterol, safety, cost-effectiveness	Uncertain publication date

RHP Red Heart Pill

Polypills in practice – where are we now?

Despite several polypills that simultaneously address more than one risk factor having been evaluated over the past decade, few have been marketed in high income countries such as Australia.[24] The exception is a combination of amlodipine besylate and atorvastatin calcium which has been available for some time, with over a million scripts written per year in Australia.[23] However, no polypills containing statins, multiple blood pressure lowering drugs or aspirin are currently available. The polypill used in the FOCUS trial has been licensed in Guatemala, and several other polypills are available in India including the polypill used in the TIPS series of clinical trials.

The regulatory pathway for polypills is currently challenging. To support an indication for prevention of cardiovascular disease in individuals without any current indications for treatment, placebo-controlled clinical trials with morbidity and mortality outcomes will be required. For use in patients with established indications for the component drugs of a polypill, complex pharmacodynamic and pharmacokinetic testing to demonstrate equivalence will be required. However, for the broadest indication of 'prevention of cardiovascular disease' in patients who are currently recommended for all components of a polypill, there remains uncertainty about whether or not large-scale clinical trials on adherence and biomarkers of adherence (e.g. blood pressure, cholesterol) will be sufficient.

Conclusion

In the last decade, significant progress has been made in testing the concept of a cardiovascular polypill. Polypills can reduce cardiovascular risk factors to the same degree as their individual components, without increasing adverse events. Long-term trials with morbidity and mortality outcomes examining the broad use of cardiovascular polypills for primary prevention are ongoing and are several years away from reporting.

Results from trials demonstrating the positive impact of a polypill-based strategy on improving the appropriate use of preventive drugs in people with established indications are already accumulating. Definitive answers are expected to be available in the next 12 months. <

The George Institute for Global Health recently secured an exclusive global license for the polypills used in the SPACE Collaboration trials, following a decision by Dr Reddy's Laboratories Ltd not to proceed with taking the products to market because of existing regulatory requirements.

The George Institute for Global Health has received funding from Dr Reddy's Laboratories to support the secretariat of the SPACE Collaboration. Ruth Webster is the coordinator of the SPACE Collaboration and Anushka Patel is the deputy chair of the SPACE Collaboration's Steering Committee. Anushka Patel is the principal investigator of the Kanyini Guidelines Adherence with the Polypill trial[9], an investigator in UMPIRE and an investigator in the Programme to Improve Life and Longevity trial.[10]

Anushka Patel and Ruth Webster have received funding from Dr Reddy's Laboratories to attend one SPACE Collaboration Investigators meeting.

Q:

SELF-TEST QUESTIONS

True or false?

1. The polypill for primary prevention of cardiovascular disease contains more than one antihypertensive drug.
2. The polypill is more effective than its individual components given alone.

Answers on page 107

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