GENERAL INFORMATION ABOUT POLYPILL OR MULTIPILL
AND MARKET FORMULATION LIKE POLYCAP

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ABSTRACT

A polypill is a medication that is a combination drug of multiple active ingredients [1]. They can often be aimed to be consumed widespread in the population, even currently healthy ones, as a means of preventive medicine. It often contains four or more active ingredients, with the intention of reducing the number of tablets or capsules (generally orally administered) that need to be taken, which in turn may facilitate handling and administration of the drug. When used for preemptive use, the dosages are naturally relatively low compared to what is administered to people already having disease or significant risk factors. The term polypill coined in 2003 by Wald and Law [2] was aimed at prevention of cardiovascular disease. The term has since gained broader acceptance, being used for other conditions as well, such as diabetes. The combination of three blood-pressure-lowering drugs at low doses, with a statin, aspirin, and folic acid (the polypill), could reduce cardiovascular events by more than 80% in healthy individuals. We examined the effect of the Polycap on blood pressure, lipids, heart rate, and urinary thromboxane B2, and assessed its tolerability.

KEYWORDS

Polypill or multipill, polycap

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INTRODUCTION

Doctors will be treating population risk rather than individual risk factor thresholds as is current mainstream practice. So, if everyone was given the "Polypill" the average blood pressure and cholesterol levels within the population would fall, thus reducing overall population risk. The "polypill" would contain three blood pressure medications at low dose.

- A diuretic such as hydrochlorthiazide
- A beta-blocker such as atenolol
- An ACE inhibitor such as lisinopril

This is combined with

- A statin such as Simvastatin
- Aspirin at a dose of 75 mg
- Folic acid

(Folic acid has been shown to reduce the level of homocysteine in the blood which is another risk factor for heart disease)

CARDIOVASCULAR POLYPILL

In their paper in 2003, *A strategy to reduce cardiovascular disease by more than 80%* by Wald and Law postulated that by using a combination of well known, cheap medications in one pill (the "Polypill") would be a particularly effective treatment against cardiovascular disease. [2] They presented a statistical model which suggested widespread use of the polypill could reduce mortality due to heart disease and strokes by up to 80%. The treatment is potentially cheap, with few side effects (in perhaps 10-15% of recipients) and the research was based on data from many trials relating to the individual components. The concepts they present are based on these principles: reducing blood pressure, cholesterol and taking a low dose of aspirin to help prevent heart disease and stroke. (In the interim, however, there is concern that the use of aspirin in a healthy population causes more harm than good [4] tests of the Wald and Law polypill have been recommended in 2005. Additionally, "polypills" are currently available in India. Any GP can currently prescribe all the components of the polypill separately for her/his patients. The ingredients of polypill are off patent since this would make the polypill quite cheap (some estimates on the BMJ rapid responses were less than 70 pounds per year), there is little financial incentive for pharmaceutical companies to pay the high costs of a clinical trial. (Naturally, however, large insurers or national healthcare systems may have considerable financial incentive to pay for such trials). The concepts they present are based on these principles: reducing blood pressure, cholesterol reducing and taking a low dose of aspirin to help prevent heart disease and stroke. (In the interim, however, there is concern that the use of aspirin in a healthy population causes more harm than good [4] Tests of the Wald and Law polypill have been recommended in 2005. Additionally, "polypills" are currently available in India. Any GP can currently prescribe all the components of the polypill separately for her/his patients. The ingredients of polypill are off patent since this would make the polypill quite cheap (some estimates on the BMJ rapid responses were less than 70 pounds per year), there is little financial incentive for pharmaceutical companies to pay the high costs of a clinical trial. (Naturally, however, large insurers or national healthcare systems insurers may have
considerable financial incentive to pay for such trials). Cardiologists in Spain are currently developing a polypill for secondary cardiovascular prevention. This project is being done in collaboration with Ferrer-Internacional, which is a Spanish pharmaceutical company based in Barcelona with experience in the development and launching of international projects. These authors believe that this polypill delivered at a low price could improve adherence to treatment, reduce the cost and make treatment affordable in low-income countries. Furthermore, they preview that success in this area of prevention could lead to the development of polypills for several other diseases, such as diabetes and stroke.

Resources

The broad concept of a polypill for cardiovascular disease has existed for decades, with early proponents coining the term "aspolol" i.e. a combination of aspirin and atenolol. Fixed dose combinations are common in other clinical areas, such as tuberculosis and HIV/AIDS. The patent granted to Wald and Law on the cardiovascular polypill has a priority date of April 4th, 2000. The Wellcome Trust and World Health Organisation convened a meeting to discuss the concept in 2001, but did not progress it at that time. The concept was mentioned by Salim Yusuf in an editorial in The Lancet in 2002. In a 2003 article in the BMJ, Wald and Law coined the term "polypill" and proposed the concept of combining six medications that have been used for decades to treat cardiovascular disease and providing this to all people with cardiovascular disease and those in Western countries aged 55 years or more. They combined the numerical results from several meta-analyses of the individual effects of these medications to produce an estimate of the overall combined effect on morbidity and mortality. Articles using similar methods have proposed other sorts of polypills, including one for diabetes (and potentially for pre-diabetes).

The Indian Polycap Study

A randomized, controlled, double-blind study called The Indian Polycap Study (TIPS), led by Salim Yusuf and Prem Pais, documented the outcome of 2,000 individuals with an average age of 54 given the medication, all of whom had at least one heart disease risk factor: diabetes, hypercholesterolemia, hypertension, obesity or smoking. During a 12-week treatment period, 400 of the study participants were given Polycap. The remainder was divided into eight groups of 200 who were given either individual components or groups of them. Three of the groups of 200 received only aspirin, simvastatin or thiazide respectively; three groups received two of the three blood pressure medications; another received all three blood pressure medications; another received all three blood pressure medications, while the last received all three combined with aspirin. The individuals who were given Polycap saw their blood pressure drop six to seven points for both their systolic and diastolic levels. These reductions in blood pressure could cut the risk
of heart disease by 62% and of stroke by 48% based on the results of other studies that showed risk reductions from cutting blood pressure levels. The combined pill was almost as effective as the individual pills with no increase in side effects.

**Treatment of Population Risk**

Wald and Law have taken the novel perspective that everyone over the age of 55 should take a pill containing medications to manage these issues irrespective of individual risk factor levels. The idea is that most people in Western Countries are at high overall risk, and the lowering risk factor levels will benefit all. Central to this is the realization that risk factors are continuously associated with risk, and the dichotomies of, for example, "hypertension" and "no hypertension" have no scientific basis\[11\]. Basically, the polypill could be used as a default medication for all people over 55 (or for others with comparable risks). Currently, individual cardiovascular risk can be calculated based on the 50-year (and still going) longitudinal study on the population of Framingham, Massachusetts (the Framingham heart study). The polypill takes a population-based approach to management. The concept of "normal" and treatment thresholds becomes less relevant when taking a population-based approach to disease control. Traditionally, the approach has been to treat only if certain risk thresholds have been reached. Paradoxically, even though an individual may not reach these traditional thresholds, benefit will still accrue by further reductions in blood pressure, cholesterol etc. This is because there is a sliding scale of risk; the concept of abnormal on one side of the line corresponding to high risk and requiring treatment, and normal on the other side, being low risk requiring no treatment is now under scrutiny. Doctors will be treating population risk rather than individual risk factor thresholds as is current mainstream practice. So, if everyone was given the "Polypill" the average blood pressure and cholesterol levels within the population would fall, thus reducing overall population risk.

**Information and Methods About Polycap\[12\]**

The combination of three blood-pressure-lowering drugs at low doses, with a statin, aspirin, and folic acid (the polypill), could reduce cardiovascular events by more than 80% in healthy individuals. We examined the effect of the Polycap on blood pressure, lipids, heart rate, and urinary thromboxane B2, and assessed its tolerability.

**METHODS**

In a double-blind trial in 50 centres in India, 2053 individuals without cardiovascular disease, aged 45—80 years, and with one risk factor were randomly assigned, by a central secure website, to the Polycap (n=412) consisting of low doses of thiazide (12.5 mg), atenolol (50 mg), ramipril (5 mg), simvastatin (20 mg), and aspirin (100 mg) per day, or to eight other groups, each with about 200 individuals, of aspirin alone, simvastatin alone,

hydrochlorothiazide alone, three combinations of the two blood-pressure-lowering drugs, three blood-pressure-lowering drugs alone, or three blood-pressure-lowering drugs plus aspirin. The primary outcomes were LDL for the effect of lipids, blood pressure for antihypertensive drugs, heart rate for the effects of atenolol, urinary 11-dehydrothromboxane B2 for the antiplatelet effects of aspirin, and rates of discontinuation of drugs for safety. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number implied by NCT00443794.

FINDINGS[13]

Compared with groups not receiving blood-pressure-lowering drugs, the Polycap reduced systolic blood pressure by 7·4 mm Hg (95% CI 6·1—8·1) and diastolic blood pressure by 5·6 mm Hg (4·7—6·4), which was similar when three blood-pressure-lowering drugs were used, with or without aspirin. Reductions in blood pressure increased with the number of drugs used (2·2/1·3 mm Hg with one drug, 4·7/3·6 mm Hg with two drugs, and 6·3/4·5 mm Hg with three drugs). Polycap reduced LDL cholesterol by 0·70 mmol/L (95% CI 0·62—0·78), which was less than that with simvastatin alone (0·83 mmol/L, 0·72—0·93; p=0·04); both reductions were greater than for groups without simvastatin (p<0·0001). The reductions in heart rate with Polycap and other groups using atenolol were similar (7·0 beats per min), and both were significantly greater than that in groups without atenolol (p<0·0001). The reductions in 11-dehydrothromboxane B2 were similar with the Polycap (283·1 ng/mmol creatinine, 95% CI 229·1—337·0) compared with the three blood-pressure-lowering drugs plus aspirin (350·0 ng/mmol creatinine, 294·6—404·0), and aspirin alone (348·8 ng/mmol creatinine, 277·6—419·9) compared with groups without aspirin. Tolerability of the Polycap was similar to that of other treatments, with no evidence of increasing intolerability with increasing number of active components in one pill.

INTERPRETATION

This Polycap formulation could be conveniently used to reduce multiple risk factors and cardiovascular risk.

Mechanism of Action and Management of Drugs

M/A of Ramiprill

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[Diagram of Renin-Angiotensin System]

- Renin Substrate
  - Renin Release From Kidney
    - Angiotensin-1
    - Angiotensin Converting Enzyme
      - Angiotensin-2
        - Non-ACE Enzymes Such as Chymase
          - AT-1 Receptor
            - Vasoconstriction
              - Aldosterone release leading to H2O and salt retention
              - Hypertrophic growth
              - Cardiac remodeling
          - AT-2 Receptor
M/A of Statin

M/A of Metformin
Management of β-blocker and NSAIDS

Polypill for Diabetes and Syndrome-X\(^{[14]}\)

Diabetes particularly Type 2 diabetes is a major cause of morbidity and mortality. Diabetes also contributes substantially to cardiovascular risk. Unfortunately, some of the ingredients in Wald and Law's original polypill may not be advisable for patients with diabetes (for example: beta-blockers - which can lead to weight gain, and thiazide diuretics). The polypill for diabetes includes:

1. A Statin. To reduce LDL cholesterol and they also have recently been shown to have anti-inflammatory properties.
2. An ACE inhibitor (for blood pressure control AND to protect the kidneys).
3. Aspirin (antiplatelet and anti-inflammatory properties), and
4. Metformin - an excellent medication for diabetes that is also associated with weight loss.

Many people who are overweight are diabetic without knowing it. Many additional people have prediabetes and may benefit from active intervention. Overall, people who have diabetes or prediabetes, high cholesterol and/or high blood pressure and are overweight are considered to have metabolic syndrome X, and may benefit substantially from the Diabetes polypill.
Perhaps, as the polypill strategy becomes widely adopted, people over 55 with a "normal" body mass index or waist circumference will take the Wald and Law polypill, and the obese or substantially overweight will take the Diabetes / Syndrome X polypill.

**Cost effectiveness**

Wald and Law's analysis predicts major cost savings and productivity gains from a polypill approach. Similarly, the Diabetes / Syndrome X polypill is estimated to save hundreds of billions of dollars.

More importantly, the human cost of these chronic diseases can be substantially reduced. When a person has a stroke, it can ruin his or her quality of life. It also places a major burden on careers. Kidney failure and dialysis (common in end-stage diabetics) is also devastating.

**Sources of resistance**[15]

**Medical expertise and Simplicity of Treatment:**-

If a polypill strategy works for a large percentage of the patient population, it may threaten some experts and specialists who might stand to lose financially (although no doubt most of these experts would be delighted by the human benefits, and would probably endorse it - despite any personal financial hardship that this might cause them). The polypill, being a simple "off-the-rack" default treatment, also reduces the sense of control and exercise of expertise that comes from prescribing individually tailored medication regimens. Unfortunately, individually tailored approaches may be more expensive and difficult and time consuming to access.

**Lifestyle Modification and "Punishing the Sinners":**-

There is a large cohort of health professionals that advocate lifestyle modification. It is held that, if a person stops smoking, exercises 30 minutes or so per day and eats a healthy diet, over time his or her risk of cardiovascular disease can be significantly lessened. Many people are resistant to this regimen, finding it too difficult, unpleasant, invasive and inconvenient to adhere to, and therefore are unable to achieve and sustain these benefits. Furthermore, there is increasing evidence that even among individuals with healthy lifestyles, some medications, like statins, can even further reduce one's cardiovascular risk. The benefits from reminding people of the benefits of lifestyle modifications and encouraging them to pursue them are generally agreed, but proponents of polypills argue that this does not justify delay of potentially highly beneficial medications like the polypill. In practice, many people above 55 will probably not observe sufficient lifestyle modifications to improve their health, and will benefit from medications such as those contained in the polypill. Excessive insistence on the lifestyle modification approach implies that "sinners" (those who are unable or unwilling to dramatically alter their lifestyle and habits) should expect to suffer for their non-compliance. This may be objected to on grounds of freedom of action, in using legal means to punish financially, or through the withdrawal of medical services, non-compliance with a prescribed regimen[16].

While individuals who prefer to observe a lifestyle modification approach should be encouraged to do so, the alternative of effective medical treatment may be beneficial to non-compliers. Cardiovascular disease and diabetes may be asymptomatic until substantial irreversible damage has occurred. This makes a dogmatic "lifestyle modification" approach
alone undesirable because it may deter vulnerable individuals from seeking prophylactic diagnosis and treatment.

**RESULTS**

The thought that people might be able to take a single pill to reduce multiple cardiovascular risk factors has generated a lot of excitement; it would certainly revolutionize heart disease prevention as we know it. The polypill showed significant reductions in blood pressure and lipids and had a good safety profile. For the trial, which lasted 3 months, researchers recruited over 2,000 healthy participants aged 45 to 80 with one cardiovascular risk factor and compared the effect of the polypill versus 8 individual drugs on blood pressure, cholesterol, heart rate, and blood plate stickiness (as measured by urinary thromboxane B2). They found that the Polycap was well tolerated and there was no evidence of side effects. They also found that the rate of stopping the polypill was the same as for individual drugs.

**CONCLUSION**

From above information, we found that the polypill is much more effective to prevent the heart attack, compare to normal single dose of any drug. The researches were found to be, the combination of five drugs have no drug interaction and they all give beneficial effects to patient to reduce the heart attack.

**REFERENCES**


