

Polypill Shows Promise for Reducing Cardiovascular Disease Risk Factors

The Indian Polycap Study. 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;373:1341–51.

Study Overview

Objective. To examine the effect and tolerability of the Polycap, a combination capsule comprised of 3 low-dose antihypertensive drugs, a statin, and aspirin, on blood pressure, lipid levels, heart rate, and urinary thromboxane B2.

Design. Double-blind randomized trial (The Indian Polycap Study [TIPS]).

Setting and participants. Between March 2007 and August 2008, 2053 individuals aged 45 to 80 years were recruited from 50 centers across India if they had no cardiovascular disease (CVD) but at least 1 of the following CVD risk factors: smoker within past 5 years, type 2 diabetes, blood pressure >140 mm Hg systolic or 90 mm Hg diastolic, abnormal lipid levels (low-density lipoprotein [LDL] cholesterol > 3.1 mmol/L or high-density lipoprotein [HDL] cholesterol < 1.04 mmol/L), or increased waist-to-hip ratio (> 0.85 for women and > 0.90 for men). Individuals were excluded if they had blood pressure > 160/100 mm Hg, were taking ≥ 2 antihypertensive drugs, were taking 1 of the study drugs, had a serum LDL cholesterol level > 4.5 mmol/L, a creatinine level > 177 $\mu\text{mol/L}$ (2.0 mg/dL), a potassium level > 5.5 mmol/L, abnormal liver function, asthma, or were pregnant or lactating. Participants initially entered a 3-week screening phase during which eligibility for the study was confirmed and baseline data were recorded. If the participant was taking any study drug that could be safely withdrawn, the participant could be included after 3 weeks.

Intervention. Before randomization, all patients underwent a clinical examination and had a 12-lead electrocardiogram, heart rate, and blood pressure recorded. Fasting blood samples were drawn for glucose, potassium, creatinine, liver function tests, and lipids. Urine was collected for 11-dehydrothromboxane B2 concentrations in 1490 individuals. Participants were randomly assigned to 1 of 9 treatment groups; pills were identical to maintain blinding. 412 participants received the Polycap, which consisted of thiazide (12.5 mg), atenolol (50 mg), ramipril (5 mg), simvastatin (20 mg), and aspirin (100 mg). The remaining participants

were randomized to 1 of 8 other groups (each with about 200 patients): aspirin alone, simvastatin alone, hydrochlorothiazide alone, 3 combinations of 2 blood pressure-lowering drugs, 3 blood pressure-lowering drugs alone, or 3 blood pressure-lowering drugs plus aspirin. To avoid hypotension in patients with normal blood pressure, a 2.5-mg dose of ramipril was used for the first 7 days and then increased to 5 mg. Study visits occurred at 10 days and then at 4, 8, 12, and 16 weeks. At 12 weeks, the study drug was discontinued and a final visit was arranged at 16 weeks, at which time all participants received advice about improving lifestyle choices to reduce CVD risk factors.

Main outcome measures. The primary outcome measures were LDL for the effect of simvastatin, blood pressure for the effects antihypertensive drugs, heart rate for the effects of atenolol, urinary 11-dehydrothromboxane B2 for the antiplatelet effects of aspirin, and rates of discontinuation of the drugs for safety. Adverse events associated with study drugs were measured. This study utilized an intention-to-treat analysis, evaluating for statistical noninferiority between the Polycap and the other groups.

Main results. Of 2053 patients enrolled, 326 patients did not complete the last study visit. Polycap reduced systolic blood pressure by 7.4 mm Hg (95% confidence interval [CI], 6.1–8.1) and diastolic blood pressure by 5.6 mm Hg (95% CI, 4.7–6.4) compared with groups not receiving blood pressure-lowering drugs. This effect was similar when 3 blood pressure-lowering drugs were used, with or without aspirin. The antihypertensive effect of each pill was greater with increasing number of component antihypertensive drugs (2.2/1.3 mm Hg with 1 drug, 4.7/3.6 mm Hg with 2 drugs, and 6.3/4.5 mm Hg with 3 drugs). The 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 [95% CI, 0.72–0.93]; $P = 0.04$). However, this effect was greater than reductions seen in groups that did not receive simvastatin ($P < 0.001$). The reductions in heart rate with Polycap and other groups using atenolol were similar (7.0 bpm), and both were significantly greater than in groups without atenolol ($P < 0.001$).

Compared with groups without aspirin, 11-dehydrothromboxane B₂ reductions were similar in patients who took the Polycap (283.1 ng/mmol creatinine [95% CI, 229.1–337.0]) compared with the 3 blood pressure–lowering drugs plus aspirin (350.0 ng/mmol creatinine [95% CI, 294.6–404.0]) and aspirin alone (348.8 ng/mmol creatinine [95% CI, 277.6–419.9]). Tolerance of Polycap was similar to other treatments, with no evidence of increasing intolerability with increasing numbers of active components in 1 pill. The rates of discontinuation of study drugs were not significantly different across the 9 groups. Specific adverse events did not differ significantly between groups. Using a simple multiplication of risk ratios estimate for the individual effects of aspirin, blood pressure lowering with 3 drugs, and simvastatin, the authors estimated that the Polycap could potentially reduce coronary heart disease by 62% and stroke by 48%.

Conclusion. Polycap is noninferior to its individual components in lowering blood pressure and heart rate. It substantially lowers LDL cholesterol and urinary 11-dehydrothromboxane B₂, but to a degree that is slightly less than that with simvastatin or aspirin alone. Whether these differences are clinically significant remains to be seen. Polycap significantly improved targeted CVD risk factors and deserves further study in a large placebo-controlled trial with hard clinical endpoints.

Commentary

CVD is the leading cause of mortality in the world, with over 80% of deaths in low- and middle-income countries attributable to CVD [1]. The burden of CVD is expected to disproportionately impact working-age adults in low- and middle-income countries, which would have an adverse macroeconomic impact in many parts of the world [2–4]. Given that the traditional Framingham risk factors for coronary artery disease (hypercholesterolemia, tobacco, hypertension, and diabetes) [5] are responsible for much of the population-attributable risk for CVD in low- and middle-income countries [6], there has been much discussion about cost-effective strategies that can be pursued at both individual and population levels to try to avert an otherwise burgeoning global CVD epidemic [7,8].

In a 2002 editorial, Yusuf [9] hypothesized that a combination pill that included aspirin, a β blocker, an angiotensin-converting enzyme inhibitor, and a lipid-lowering agent could, in theory, reduce the risk of recurrent cardiovascular events by nearly 75%, based on the results of numerous randomized controlled trials and meta-analyses that had previously demonstrated the efficacy of the individual components. Wald and Law [10] formalized and expanded this hypothesis in 2003 and originally coined the term “polypill.” Their original formulation contained aspirin, 3 antihypertensive agents at half-standard dose, a statin, and

folic acid. Their model yielded estimates of a nearly 80% reduction in recurrent cardiovascular events as well as more than a decade of event-free survival for individuals aged older than 55 years without CVD. Interest in the polypill has increased since that time, and there are now several different formulations and combinations in the process of development and testing [11]. In addition, recent work has demonstrated that a multidrug regimen could be cost-effective in low- and middle-income countries for both primary and secondary prevention of CVD [12].

Despite this increasing interest and investment in the polypill, several questions remain: (1) Can a combination pill be formulated into a chemically stable compound suitable for oral administration? (2) Would a combination pill yield similar efficacy results as the individual components administered separately? (3) Would a combination pill be well tolerated? (4) Can low-dose antihypertensive agents be safely administered to individuals with normal blood pressure? (5) Can a combination pill be distributed widely and inexpensively to optimize access to individuals in low- and middle-income countries? (6) Is a combination pill more appropriate for primary or secondary prevention of CVD? (7) What is the optimal balance between pharmacotherapeutic and lifestyle modification approaches to CVD prevention in the context of the global CVD epidemic? TIPS investigators sought to answer a few of these important questions. Specifically, they aimed to demonstrate the noninferiority of the Polycap relative to its components, both individually and in combination, with respect to changes in risk factor levels. In addition, the tolerability of the Polycap was compared with its components, and drug-drug interactions were monitored.

TIPS researchers found that the Polycap was equally efficacious in lowering blood pressure and heart rate as its individual components. Polycap also significantly lowered LDL cholesterol and urinary 11-dehydrothromboxane B₂ (an indirect measure of blood-clotting ability), but somewhat less than simvastatin or aspirin alone. The Polycap was well tolerated with similar adverse event and discontinuation rates as compared with the other formulations. No major drug-drug interactions were seen beyond a slight reduction in efficacy for simvastatin in the combinations. The use of a triple combination of antihypertensive agents did not lead to significantly higher rates of hypotension or bradycardia in normotensive individuals. This study was well designed and medications were distributed across a 50 medical centers in India without major logistical difficulties. Finally, the study investigators calculated a substantial total decrease in theoretical CVD burden based on the observed short-term changes in risk factors (potentially reducing coronary heart disease and stroke by 62% and 48%, respectively).

TIPS had a number of strong features. It was a large randomized study conducted in real-world settings across 50 sites in India, thereby increasing its external validity to settings across the developing world where few CVD prevention trials have been conducted but are urgently needed. The use of 9 treatment groups allowed comparisons of different medication combinations and interactions. Finally, the researchers used well-validated measures to assess biological risk factor reduction.

A number of limitations deserve mention. Data on blood pressure and lipid levels were not available for 4% and 9% of patients, respectively. Additionally, nearly 25% of patients in the combined antihypertensive group and more than 15% of patients in the Polycap group prematurely stopped taking the medications, mainly for “social reasons.” Considering the short follow-up period of only 12 to 16 weeks, this dropout rate should be a source of concern for future polypill trials. The dose of simvastatin used in the Polycap (20 mg) was half the dose modeled by Wald and Law [10]; thus, a direct comparison is difficult. The only combination regimen with a statin was the Polycap. Given their potency and low cost, future studies with alternative statin-containing combination formulations would be helpful to assess, for example, the relative benefit of an aspirin plus a statin compared with different antihypertensive-statin combinations. Finally, the trial was sponsored by the maker of the Polycap, although it does not appear that they had a role in analyzing or reporting the results.

TIPS has a number of important implications. First, it delivers the first well-documented evidence that a polypill is feasible, efficacious, and tolerable in a developing world clinical setting. The ability to manufacture an efficacious combination pill at (hopefully) low cost is crucial, given the poor availability and high cost of individual CVD medications across the developing world [13]. The relatively poor short-term adherence reported in TIPS may be a problem for future polypill interventions that target populations that may resist taking chronic medications for theoretical preventive benefits. Questions remain on whether the polypill will steal the focus from other crucial behavioral modification interventions for smoking, obesity, and physical activity and whether use of the polypill will implicitly medicalize a constellation of diseases that largely stem from changing human environments, aggressively marketed addictions (tobacco), and unhealthy food options. Although the Polycap formulation studied in TIPS was efficacious, it is unknown whether this is the best formulation. Answers to this question will require many studies that evaluate multiple combinations while assessing hard clinical endpoints. These trials will take years to complete and be published. In the interim, should safe components of the polypill that show great promise to reduce disease (eg, statins) be promoted instead? Novel risk scores based on measurements that

can be performed in low-resource settings without laboratories were shown to perform nearly as well as their more expensive counterparts and hold promise for future risk stratification efforts [14]. Wald and Law’s original proposal [10] essentially advocated a radical change in the prevention paradigm from tailored therapy based on individually determined degree of risk to a standardized, generic intervention given in an indiscriminating fashion to an entire group of people. Future studies will need to shed light on how the polypill should be used in the most cost-effective, high-impact fashion for appropriate target populations.

Applications for Clinical Practice

The Polycap appears to be safe, well tolerated, and generally equal in efficacy to its individual components. It is an intriguing intervention that holds great promise for CVD prevention across the developing world. However, like so many previous promising interventions, Polycap requires validation of effect in a large-scale outcomes study.

—Review by Rajesh Vedanthan, MD, MPH (Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai Medical Center, New York, NY) and Asaf Bitton, MD

References

1. Lopez AD, Mathers CD, Ezzati M, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006;367:1747–57.
2. Abegunde DO, Mathers CD, Adam T, et al. The burden and costs of chronic diseases in low-income and middle-income countries. *Lancet* 2007;370:1929–38.
3. Gaziano TA. Economic burden and the cost-effectiveness of treatment of cardiovascular diseases in Africa. *Heart* 2008;94:140–4.
4. Leeder S, Raymond S, Greenberg H. A race against time: the challenge of cardiovascular disease in developing economies. New York: Trustees of Columbia University; 2004.
5. Wilson PW, D’Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97:1837–47.
6. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937–52.
7. Asaria P, Chisholm D, Mathers C, et al. Chronic disease prevention: health effects and financial costs of strategies to reduce salt intake and control tobacco use [published erratum appears in *Lancet* 2007;370:2044–53]. *Lancet* 2007;370:2044–53.
8. Lim SS, Gaziano TA, Gakidou E, et al. Prevention of cardiovascular disease in high-risk individuals in low-income and middle-income countries: health effects and costs. *Lancet* 2007; 370:2054–62.
9. Yusuf S. Two decades of progress in preventing vascular disease [editorial]. *Lancet* 2002;360:2–3.
10. Wald NJ, Law MR. A strategy to reduce cardiovascular

- disease by more than 80% [published errata appear in *BMJ* 2003; 327:586 and 2006;60:823]. *BMJ* 2003;326:1419.
11. Guglietta A, Guerrero M. Issues to consider in the pharmaceutical development of a cardiovascular polypill. *Nat Clin Pract Cardiovasc Med* 2009;6:112–9.
 12. Gaziano TA, Opie LH, Weinstein MC. Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. *Lancet* 2006;368:679–86.
 13. Mendis S, Fukino K, Cameron A, et al. The availability and affordability of selected essential medicines for chronic diseases in six low- and middle-income countries. *Bull World Health Organ* 2007;85:279–88.
 14. Gaziano TA, Young CR, Fitzmaurice G, et al. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. *Lancet* 2008;371:923–31.

Copyright 2009 by Turner White Communications Inc., Wayne, PA. All rights reserved.