Cardiovascular Disease Prevention Using Fixed Dose Pharmacotherapy in Iran: Updated Meta-Analyses and Mortality Estimation

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Abstract

Background: Short term randomized trials have shown the effectiveness of a fixed dose combination therapy (known as Polypill) on reducing blood pressure and serum cholesterol but the impact of Polypill on cardiovascular disease risk or mortality has not yet been directly investigated. Previous studies combined the effects of each component assuming a multiplicative joint risk model that may have led to overestimating the combined effects. We conducted an updated meta-analysis of randomized trials of anti-hypertensives, statins and aspirin. We used the estimated effect sizes applying a more conservative assumption to estimate the number of ischemic heart disease (IHD) and stroke deaths that could have been averted by Polypill in Iranians aged 55 years or older in 2006.

Methods: We searched Medline and reviewed previous meta-analyses to select randomized trials on Angiotensin Converting Enzyme-inhibitors, thiazides, aspirin, and statins. We used a random-effects model to pool relative risks for each component and estimated the joint relative risks using multiplicative and additive assumptions for 4 combinations of Polypill components. We used age-cause-specific mortality, separately by gender, and estimated the number of preventable deaths from IHD and stroke.

Results: Under the additive joint RR assumption, the standard Polypill formulation was estimated to prevent 28500 (95% CI: 21700, 34100) IHD deaths and 12700 (95% CI: 8800, 15900) stroke deaths. Removing aspirin from the combination decreased preventable IHD deaths by 15% under the additive assumption (5600 deaths) and by 21% under the multiplicative assumption (6800 deaths) and reduced preventable stroke deaths under both additive and multiplicative assumptions by 3% (300 deaths). There was no significant difference between Polypill combinations with anti-hypertensive agents in full-dose or half-dose.

Conclusion: Polypill can prevent a large number of IHD and stroke deaths in Iran. The cost-effectiveness, feasibility, and acceptability of this prevention strategy remain to be investigated.

Keywords: Cardiovascular diseases, drug combinations, Polypill, primary prevention, risk factors

Introduction

Cardiovascular diseases (CVDs) are the leading causes of death in both high-income countries and in most developing countries outside sub-Saharan Africa.1-3 Mortality from CVD has declined sharply in most developed countries in the past 3-4 decades.4,5 Where it has been studied, almost half of this decline was attributed to improved treatment of cases and the remaining half to changes in risk factors such as systolic blood pressure, smoking and dyslipidemia.4,5 Considering the high levels of exposure to these risk factors in many developing countries,6-8 efforts to monitor and control them may have a substantial effect on preventing CVD mortality and burden. One possible intervention is a fixed-dose combination therapy.

The potential of fixed-dose combination pharmacotherapy for CVD prevention (composed of anti-hypertensive agents, aspirin, and a statin) was first discussed in the World Health Organization (WHO) and Wellcome Trust meeting in 2001.9 The possible public health impact and cost-effectiveness of enhanced access to the combination treatment was also mentioned in the World Health Report 2002.10 In a widely cited paper in 2003 which coined the term “Polypill”, Wald and Law estimated that more than 80% of CHD deaths can be prevented in adults 55 years old or older.11 A few short-term randomized trials have examined the effectiveness of the Polypill on risk factors reduction and its tolerability.12-14 However, the effect of Polypill on the risk of CVD has not yet been reported and the current evidence has been generated by multiplying the individual effects of the components of Polypill which may have led to overestimating the joint effect. Furthermore, it is not clear if the results of the randomized trials of the components of Polypill which are all conducted in developed countries are generalizable to a developing country like Iran because the trial population may have been quite different from the general population of Iran with respect to important study characteristics. Finally, a few large and well-conducted randomized trials of statins and aspirin (such as JUPITER15 and Women’s Health Study16) have...
been recently published and were not included in the Wald and Law analysis.

Therefore, we conducted an updated meta-analysis of randomized controlled trials of effectiveness of the components of Polypill in primary prevention of CVD. We used the estimations for effect size of Polypill and estimated the number of CVD deaths that could be prevented by Polypill in Iran using a more conservative approach and also attempted to standardize the effects to the Iranian population.

Materials and Methods

Study Design

We estimated the relative risks (RRs) of ischemic heart disease (IHD) and stroke in healthy individuals that would be treated with Polypill versus those assigned to usual care or placebo. The components of Polypill we considered in our study included aspirin, two anti-hypertensive agents (ACE-inhibitors and thiazides), and a statin. We derived the best current estimate of the RRs for each component of Polypill from meta-analyses of randomized trials of primary prevention and computed multiplicative and additive RRs for the joint effect of the 3 components. Finally, we estimated the number of deaths that would have been prevented by administering the Polypill to men and women 55 years or older in Iran in 2006.

Our analysis included three main steps: 1) conducting systematic reviews and meta-analyses to estimate the individual RRs for each component of Polypill; 2) estimating the joint RRs for all components under different joint risk assumptions; and 3) estimating the number of preventable deaths due to IHD and stroke.

Systematic review and meta-analyses

We searched Medline (via PubMed) for clinical trials and meta-analyses on aspirin published from 2001, and ACE-inhibitors and thiazides published from 2007 until the end of 2010. For trials published before the range of dates in our search strategy, we used trials identified by Law et al for anti-hypertensive agents in 2009 and by Antithrombotic Trialists’ Collaboration for aspirin in 2002. For statins, we included the trials identified in a recently conducted systematic review by one of the authors.

Two authors (SGS and EJ) reviewed the abstracts of all relevant randomized trials and meta-analyses. Discrepancies were resolved by consensus or by referring to a third author (GD). We excluded trials in which the randomization method was not acceptable; trials that did not have one arm for treatment with anti-hypertensive or aspirin or statins only; trials with another intervention (such as percutaneous coronary interventions) as the control group; trials on comparative efficacy of different drugs or on dose-response analysis of a single drug; trials on short-term effects (peri-procedural, in-hospital effects with follow-ups of 6 months or less); trials that had not reported clinical endpoints; trials in which more than 30% of study subjects had presented with a previous history of coronary heart disease or cerebrovascular disease; trials on patients with defibrillators, heart failure, familial hypercholesterolemia or chronic kidney disease; extended follow-up or post-hoc analyses of previously published trials; trials in which intention-to-treat analysis was not reported; and finally trials in which the dose of the antihypertensive agent was not within the standard range recommended by the Joint National Committee.

The outcomes of interest included fatal, non-fatal, or a combination of fatal and non-fatal IHD and stroke. Data were extracted into standard data extraction sheets. Extracted data included sample size, number of events in the treatment and control arms, and reported RRs and their 95% confidence intervals. Where data was available, RRs were extracted by sex, age or other characteristics of the study population at baseline. We also recorded the method of blinding, eligibility and exclusion criteria, compliance to treatment in each or both arms, median and maximum follow-up time, and proportion of loss to follow-up.

We used a random-effects model to pool RRs for each component of Polypill for IHD. We used the Egger’s test to evaluate publication bias in each meta-analysis and used meta-regression to evaluate the possibility of effect modification by date of publication or dose of medication for antihypertensive agents - categorized into high or low within the standard range.

We also examined differences in pooled RRs between fatal outcomes, non-fatal outcomes, and the combination of both. As the differences were not statistically significant and to achieve a higher precision, we used RRs for fatal and non-fatal outcomes combined. If RRs for combined fatal and nonfatal outcomes were not reported (which occurred in 3 studies), we used the RRs for either fatal or non-fatal outcomes, whichever was reported, in descending order of preference.

Estimating joint relative risks

We calculated multiplicative and additive joint RRs assuming that the RR for each component did not depend on the other components (i.e. no effect measure modification in the multiplicative scale). The following formulas were used for calculating joint RRs:

\[
\text{Multiplicative joint RR} = \prod_{i=1}^{n} RR_i
\]

\[
\text{Additive joint RR} = 1 / \left( \sum_{i=1}^{n} \left( \frac{1}{RR_i} - 1 \right) + 1 \right)
\]

We considered 3 different formulations of Polypill depending on the type and dosage of the anti-hypertensive agents: 1) an ACE-inhibitor in full dose plus aspirin and a statin; 2) a thiazide in full dose, aspirin, and a statin; 3) an ACE-inhibitor in half dose, a thiazide in half dose, aspirin and a statin (as administered in the trial by Malekzadeh et al.). The combination of two anti-hypertensive agents in half dose was to emulate the effect of the Polypill used in previous meta-analyses and in a current trial. We assumed a log-linear RR to estimate the effect of anti-hypertensive agents in half dose. Considering the clear evidence on side effects of aspirin, notably gastrointestinal bleeding and hemorrhagic stroke, we repeated the third scenario without aspirin. We estimated the variance of the joint relative risks assuming independence of RRs from different studies. All meta-analyses were conducted using the metan command in STATA version 11.0 (StataCorp, College Station Texas) and joint RRs and their uncertainty intervals were calculated using R version 2.11.1.

Estimating preventable deaths

We used the cause-specific mortality data at the national level, separately for each sex and age, to estimate the number of deaths that could have been averted by Polypill in Iran in 2006. Mortality data were derived from the vital registration system which does not include the mortality of Tehran. We used data from Tehran’s...
central cemetery to overcome this limitation. Because the coverage of the vital registration system is incomplete,27 we used the Synthetic Extinct Generations method to examine and correct the incompleteness of death registration. The details of methods and assumptions have been described elsewhere.28 Finally to estimate number of preventable deaths we multiplied them by total mortality due to IHD and stroke:

\[
\text{Preventable deaths} = \text{RR} \times \text{Total deaths due to IHD or stroke}
\]

Results

Our search yielded 2398 titles for randomized trials of anti-hypertensive agents or aspirin. Another 454 trials were included by reviewing previous meta-analyses. Out of the aforementioned trials, 248 trials were selected. After full text review we included 6 primary prevention trials of aspirin, 21 trials of anti-hypertensive (Figure 1), and 11 trials of statins.21 The selected studies and their characteristics are presented in Webtables 1 – 4. Only 3 statin tri-

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Agent</th>
<th>Number of Studies</th>
<th>Pooled Relative Risk</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Heart</td>
<td>Aspirin</td>
<td>6</td>
<td>0.81 (0.67, 0.99)</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitor</td>
<td>7</td>
<td>0.86 (0.79, 0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Thiazide</td>
<td>13</td>
<td>0.86 (0.76, 0.98)</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>Statin</td>
<td>11</td>
<td>0.68 (0.59, 0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>Aspirin</td>
<td>6</td>
<td>0.98 (0.84, 1.14)</td>
<td>0.768</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitor</td>
<td>8</td>
<td>0.88 (0.77, 1.01)</td>
<td>0.075</td>
</tr>
<tr>
<td></td>
<td>Thiazide</td>
<td>12</td>
<td>0.60 (0.55, 0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Statin</td>
<td>7</td>
<td>0.79 (0.66, 0.94)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Table 1. Pooled relative risks of mortality from ischemic heart disease and stroke in the treatment arm versus the control arm of randomized trials

<table>
<thead>
<tr>
<th>Polypill Components</th>
<th>Outcome</th>
<th>Multiplicative RRs</th>
<th>Additive RRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>An ACE-inhibitor in full dose, aspirin, and a statin</td>
<td>IHD</td>
<td>0.47 (0.37, 0.61)</td>
<td>0.54 (0.45, 0.64)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>0.66 (0.52, 0.90)</td>
<td>0.70 (0.57, 0.87)</td>
</tr>
<tr>
<td>A thiazide in full dose, aspirin, and a statin</td>
<td>IHD</td>
<td>0.48 (0.36, 0.63)</td>
<td>0.54 (0.44, 0.65)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>0.48 (0.36, 0.59)</td>
<td>0.51 (0.44, 0.60)</td>
</tr>
<tr>
<td>An ACE-inhibitor in half dose, a thiazide in half dose, aspirin, a statin</td>
<td>IHD</td>
<td>0.49 (0.38, 0.63)</td>
<td>0.54 (0.45, 0.65)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>0.57 (0.44, 0.74)</td>
<td>0.61 (0.51, 0.73)</td>
</tr>
<tr>
<td>An ACE-inhibitor in half dose, a thiazide in half dose, and a statin</td>
<td>IHD</td>
<td>0.60 (0.51, 0.70)</td>
<td>0.63 (0.54, 0.72)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>0.58 (0.47, 0.71)</td>
<td>0.62 (0.53, 0.72)</td>
</tr>
</tbody>
</table>

Table 2. Joint relative risks (RRs) under multiplicative and additive models
als had reported RRs by age and sex and only 2 thiazides trials reported RRs by sex. Therefore, we were unable to perform subgroup analyses or standardize the RRs to the Iranian population (see limitations in the Discussion).

The results of the meta-analyses for each component of Polypill are presented in Table 1. Except for effect of aspirin on stroke, all other effect sizes were significant at the 0.10 level (P-value for the test of heterogeneity was larger than 0.1, except for trials on aspirin). The meta-analysis showed statistically significant reductions in IHD with aspirin, ACE inhibitor, thiazide and statins and also that there were significant reductions in stroke with ACE inhibitor, thiazide and statins at 0.10 (but not with aspirin). The forest plots are presented in Web Appendix 1. We did not find a strong evidence for publication bias for any of the meta-analyses: the P-values for Egger’s test ranged from 0.07 to 0.75. The publication year and the dose of medication (high or low) did not change the relative risks significantly. The P values for the coefficient of publication year ranged from 0.13 to 0.91 and the one for dose of medication ranged from 0.29 to 0.97 across different components of Polypill.

The joint RRs for the four formulations of Polypill are presented in Table 2. RRs ranged from 0.47 to 0.68 using the multiplicative assumption and from 0.51 to 0.70 using the additive assumption. The confidence intervals for different RRs overlapped substantially across different Polypill formulations. In particular, comparing various combinations of antihypertensive drugs at full or half dose, the joint RRs did not differ substantially except possibly for stroke and antihypertensives where the effect of a full dose of thiazides seemed slightly stronger than the effect of ACE inhibitors or half dose of thiazide and half dose of ACE inhibitors combined. There were 62000 IHD deaths (34700 in men and 27300 in women) and 32500 stroke deaths (16600 in men and 15900 in women) in 2006 in Iran. Figure 2 presents the number of IHD and stroke deaths that could be prevented with a complete coverage of different formulations of Polypill. Using the more conservative additive joint RR assumption, Polypill formulation used in Malekzadeh et al’s trial (an ACE-inhibitor and a thiazide each in half dose, aspirin and a statin) was estimated to prevent 28500 (95% CI: 21700, 34100) IHD deaths and 12700 (95% CI: 8800, 15900) stroke deaths. The same formulation could prevent a total of 49600 (95% CI: 31400, 56600) IHD or stroke deaths under a multiplicative joint RR as-
The number of IHD deaths that could be averted ranged from 28500 to 32900 but did not differ significantly between different formulations and under both additive and multiplicative assumptions. The number of averted stroke deaths was smallest under the additive assumption for the combination of an ACE-inhibitor in full dose, aspirin, and a statin (9800, 95% CI: 4200, 14000), and largest under the multiplicative assumption for the combination of a thiazide in full dose, aspirin, and a statin (16900, 95% CI: 13300, 20800). Almost a third of the averted IHD deaths (32%) occurred in men below the age of 70. The same proportion in women was 25.5%. For stroke, 24% of averted deaths in men and 22.5% in women occurred below the age of 70.

Removing aspirin from the combination reduced the number of averted IHD deaths in the standard formulation (aspirin, a statin, and both antihypertensive agents in half dose) by 15% under the additive assumption (5600 deaths) and by 21% under the multiplicative assumption (6800 deaths). In contrast, removing aspirin reduced the average number of averted stroke deaths under both additive and multiplicative assumptions by 3% (300 deaths).

Discussion

Our results suggested that full coverage of Polypill in Iranian adults can reduce mortality from IHD and stroke by 30 – 53% and therefore prevent at least 28500 (95% CI: 21700, 34700) IHD deaths and 9800 (95% CI: 4200, 14000) stroke deaths in 2006. For each IHD or stroke death averted in women 1.4 deaths could be averted in men. One in three premature deaths (deaths occurring before the age of 70) from IHD and one in four premature deaths from stroke could be averted by Polypill.

The proportional effect of Polypill estimated in our analysis is much smaller than the previously reported 88% reduction in risk of IHD and 80% reduction in risk of stroke. Apart from the difference in the assumption regarding joint relative risks (multiplicative in the previous analysis versus additive in our main analysis), there are several other reasons for the differences between these two estimates: Wald and Law based their estimated reduction in risk on a relatively ambitious reduction in serum LDL cholesterol of 1.8 mmol/L after using statins for two years which is much larger than the 0.46 mmol/L reduction observed in a pilot Polypill trial that used twice the statin dose for one year. As for aspirin, Wald and Law had included trials on people with a history of IHD and which explains the larger estimates of the protective effect of aspirin compared with ours. Wald and Law estimated the risk reduction using a combination of 3 hypertensive agents as opposed to 2 agents in our analysis and also included a potential protective effect for folic acid, which has been questioned in more recent randomized trials and has not been considered in randomized trials of Polypill.

Although we used an additive assumption to generate more conservative estimates of the potential impact of Polypill, our
estimates may still be larger than what could be achieved in the general population due to imperfect adherence. Adherence to treatment in the general population is usually lower than that observed in well-controlled randomized trials which sometimes use a run-in phase to exclude possibly non-adherent individuals. For example, a recent systematic review of statins reported that adherence to treatment in several primary prevention randomized trials was on average 79% compared with 59% in two observational studies.21

Potential side effects of Polypill have to be considered. Statins may cause a mild elevation of Alanine Transaminase in about 10% of recipients and in 1 – 3% of patients elevations are more than three times the upper limit normal.31 However, the role of statins in causing liver damage is still unclear.32,33 There is also a small but important increase in risk of severe muscle damage in statin users.34,35 Furthermore, two recent meta-analyses of randomized trials found that statins may slightly increase the risk of type 2 diabetes.36,37 Aspirin increases the risk of gastrointestinal bleeding and hemorrhagic stroke which may balance out some of the protective effects on IHD and ischemic stroke. Our results indicated that removing aspirin from the formulation of Polypill will reduce the protective effects on IHD but substantial benefits still remain.

The strengths of our study can be summarized as follows. We focused on primary prevention, and used both additive and multiplicative assumptions to estimate the effect of different combinations of components in Polypill. We also considered full versus half dosage for the antihypertensives. We used the most recent cause-specific mortality data at the national level in Iran and corrected these numbers for incompleteness of death registration. Finally, we quantified uncertainty by combining sampling uncertainty in RRs and estimation uncertainty in cause-specific mortality numbers.

Our study had several limitations as well. We could not conduct the planned subgroup analyses to estimate the effect of components of Polypill by age and sex and other study characteristics due to insufficient number of trials that reported RRs by subgroup. This problem masks the effect of competing cause of mortality that could be addressed using Markov chain model or risk-deleted life expectancy. Furthermore, five out of 8 trials on ACE-inhibitors and all (except for one) trials on thiazides included in our study also used beta-blockers and calcium channel blockers to achieve the target blood pressure reduction. Therefore, our RRs for thiazides and ACE-inhibitors overestimate the effect of a single drug at full dose or two drugs at half dose without dose titration.

In summary, using Polypill for primary prevention of CVD in adults aged 55 or older may prevent half of IHD deaths and 43% of stroke deaths in Iran. Further research is required to estimate the cost-effectiveness of a large-scale population-based intervention and a detailed comparison of various treatment strategies to minimize the potential risks. In a recent study in the Netherlands, the estimated incremental cost-effectiveness ratios for treating people with a 10-year risk of CVD above 5% was €7,900 per QALY; however, similar estimates for developing countries in a previous study have been much lower (1039 – 1221 US$ per QALY).38 Lim et al found that over a 10-year period administering Polypill to the high-risk population in 23 low- and middle-income countries could avert a fifth of CVD deaths with an average annual cost per head of less than 2 US$ in Iran.39 Currently, Polypill is being manufac-

**Figure 4.** Pooled relative risks of mortality from stroke. A) ASA  B) ACE-inhibitors  C) Thiazides  D) Statins
tured by Iranian pharmaceutical companies and costs about 5 cents per pill and can in principle be administered through the extensive primary health care network.

Author Contributions
GD and FF designed the study. SGS and EJ conducted the systematic reviews and meta-analyses. FF provided the mortality data and estimated the additive and multiplicative relative risks. SGS wrote the first draft of the manuscript. GD oversaw the conduct of the study and is the study guarantor.

Acknowledgments
The authors would like to thank Professor Reza Malekzadeh, Dr. FarinKamangar, and Dr. HosseinPoustchi for their supports of the conceptualization of the study.

References

Archives of Iranian Medicine, Volume 15, Number 9, September 2012 537