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 assumption 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- and 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 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 (CVD) are the leading causes of death in both high-income countries and in most developing countries outside sub-Saharan Africa.1,2 Mortality from CVD has declined sharply in most developed countries in the past 3 – 4 decades.3,4 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.5,6 Considering the high levels of exposure to these risk factors in many developing countries,7,8 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 2001.11 The possible public health impact and cost-effectiveness of enhanced access to the combination treatment was also mentioned in the World Health Report 2002.12 In a widely cited paper in 2003 which coined the term “Polypill”, Wald and Law estimated that more than 80% of CVD deaths can be prevented in adults 55 years old or older.13 A few short-term randomized trials have examined the effectiveness of the Polypill on risk factors reduction and its tolerability.14-16 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 JUPITER17 and Women’s Health Study18) 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 were aspirin, two anti-hypertensive agents (Angiotensin-Converting Enzyme (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 de-fibrillators, 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 of antihypertensives in which the dose of the 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 was 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 with 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.

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:

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

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

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. 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 metaan 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 group, 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 deaths in Tehran. We used data from Teh-
Finally, to examine and correct the incompleteness of death registration, the Synthetic Extinct Generations method was used. The details of methods and assumptions have been described elsewhere.28 We used ran’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

Preventable deaths = joint RR * Total deaths due to IHD or stroke

**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>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 2.** Joint relative risks (RRs) under multiplicative and additive models

<table>
<thead>
<tr>
<th>Polypill Components</th>
<th>Outcome</th>
<th>Multiplicative RR</th>
<th>Additive RR</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>0.65 (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>

**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 were selected in the first round. 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

![Figure 1. Flowcharts for systematic reviews of aspirin (A) and anti-hypertensive agents (B)]
Figure 2. Pooled relative risks of mortality from ischemic heart disease. **A)** Aspirin **B)** ACE-inhibitors **C)** Thiazides **D)** Statins

Statin trials had reported RRs by age and sex and only 2 thiazide 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 figure 2 and 3. 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 4 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 assumption.

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.13 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.14 As for aspirin, Wald and Law had included trials on people with a history of IHD and patients with atrial fibrillation as well as those on healthy adults, which explains the larger estimates of the protective effect of aspirin compared with ours.13 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,28 which has been questioned in more recent randomized trials38 and has not been considered in randomized trials of Polypill.14–16

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.32 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

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**Figure 3.** Pooled relative risks of mortality from stroke. A) Aspirin  B) ACE-inhibitors  C) Thiazides  D) Statins
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 antihypertenives. 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 standardize the effect of components of Polypill to the Iranian population by age and sex and other study characteristics due to insufficient number of trials that reported RRs by subgroup. Our estimates of 'preventable deaths' ignore the competing causes of mortality that could be addressed using a Markov model or life tables. 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).

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. Currently, Polypill is being manufactured by Iranian pharmaceutical companies and costs about 5 cents.

Figure 4. The number of preventable deaths and their 95% uncertainty intervals. ACE: Angiotensin Converting Enzyme, ASA: Acetyl Salicylic Acid.
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

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Author and year (study acronym) | Study population | Exclusion criteria | Intervention groups | Outcome of interest | Follow-up | Compliance
--- | --- | --- | --- | --- | --- | ---
Furberg 1994 (ACAPS) | 519 asymptomatic man and women, 40 to 79 years old, with early coronary artery disease as defined by 5-mode ultrasonography and LDL cholesterol between the 50th and 90th percentiles, mean age 61.7 years and 51.5% male | History of MI, stroke, or angina | Losartan 20–40 mg or placebo | Non-fatal MI, any CHD | Mean 2.86 years | 77% in both arms
Dumes 1998 (ACAPS/TAPS) | 885 men and 975 women 45 to 75 years old with average TC and LDL and below-average HDL: C fall attributed to nutrition, age, claudication, CHD, or TIA | Uncontrolled HTN, secondary hyperlipidemia, or type 1 or type 2 DM that was either managed with insulin or glycosylated with glycylated-hemoglobin >10%, a body weight of more than 30% greater than the desirable limit for the height | Losartan (20–40 mg) or placebo in addition to a low-saturated fat, low-cholesterol diet | Any CHD | Mean 5.2 years | 71% in treatment arm and 65% in control arm
ALLHAT-LLT 2002 | Average age 71 years, 45 to 75 years old with average TC and LDL and below-average HDL: C fall attributed to nutrition, age, claudication, CHD, or TIA | Currently receiving lipid-lowering therapy, taking large doses of statins, or taking Pravastatin in the last year; known to be intolerant of exercise, or known significant loss of kidney function (cystine < 50 ml/day, or serum creatinine >3.5 mg/dl), or left- or right-side effects. | Paroxetine 40 mg or usual care | Total and non-fatal CHD, any CHD, fatal and non-fatal stroke, any stroke | Mean 4.8 years | 75% in control arm and 60% in treatment arm
Koomen 2002 (ASPEN) | 2410 patients with type 2 DM for 3 years or more and LDL > 3.3 mmol/L (if history of MI or interventional procedure and < 4.1 mmol/L (norm), TG-800 mmol/L (norm), LDL > 3.3 mmol/L | 1 + type 2 DM, interventional procedure or episode of unstable angina less than 3 months before screening, SBP > 190 mm Hg, active liver disease or hepatic dysfunction, or other medical condition, CHP treated with digoxin, C3+ times upper limit for HPB-190 100 mm Hg, DM > 150 mm Hg, alcohol or drug abuse, history of study medications, current or planned pregnancy, placenta or non-complete, <.90%, use of excluded medications | Losartan 10 mg or placebo | Any CHD, any stroke | Mean 4 years | 67.5% in treatment and 57.6% in placebo
Hallblad 2001 (SCAPS) | 765 men and 49 to 70 years old with diabetes and the right coronary artery but with no symptoms of CAD, mean age 61 ± 9.3 years | History of MI, angina, stroke, or essential hypertension (SBP > 180 mm Hg) or other included conditions, any other chronic or serious illness, or treatment with specific drugs, including certain drugs, other treatments, agents or medicines containingaramel drugs | Losartan 45 mg or placebo | Any CHD, any stroke | Mean 3 years | 79% in treatment and 77% in placebo
Annemans 2002 (FARTY) | 360 patients with TC > 2.28 mmol/L, aged 30–69, mean age 46 ± 13.3 years | 1 + type 2 DM, interventional procedure or episode of unstable angina less than 3 months before screening, Hct > 50%, active liver disease or hepatic dysfunction, severe renal disease (GFR < 90 liters/day), alcohol or drug abuse, history of study medications, current or planned pregnancy, placenta or non-complete, <.90%, use of excluded medications | Perindopril 10 mg or at least alone | Fruconal low, any CHD | 2 years -
Ando 2005 (OCTUS) | 158 drug-naive asymptomatic men aged 40–76 years with TC 4.5–8.9 mmol/L, TG > 1.5 mmol/L, BMI 25–35 kg/m2, and a solitary failure | Any symptomatic CVD, unstable angina, stroke, CHD ≥ 3 DM, history of surgery intervention, need for minimally invasive therapy, or other critical or unstable conditions, any other chronic or serious illness, or treatment with specific drugs, including certain drugs, other treatments, agents or medicines containingaramel drugs | Fruconal 80 mg or flutikyn in 2 to 2 factorial design | Any CHD | 4 years -
Rilke 2002 (EUPHR) | 1780 patients including men over 50 and women over 60 without history of CVD and LDL 3.3 mmol/L and CRP 2 mg/L and triglycerides > 500 mmol/L | Patients with previous coronary artery disease, hypertension, or polyvascular USS evidence of disease progression, light CK, severe high density level, uncontrolled HTN, cancer, any other diabetes, no preoperative or postoperative complications, or years from preoperative to postoperative complications | Rosuvastatin, 20 mg or matching placebo | Non-fatal MI, any CHD, any stroke | Maximum 5 years, median 1.8 years -
Nakamura 2006 (MEGA) | 6324 hypertensive elderly men (total cholesterol 5.6–9.8 mmol/L) and history of CHD, men and premenopausal women aged 40–59 | Total cholesterol < 8.6 mmol/L and triglycerides < 1.7 mmol/L in treatment group and < 8.6 mmol/L and triglycerides < 1.7 mmol/L in control group | Placebo-20 mg and diet vs diet alone | Placebo, non-fatal MI, any CHD | Mean 5.3 years | 89% in treatment arm
Shepherd 1999 (WOSCOPS) | 6895 men, age 44 to 84 years, with a mean plasma TC of 7.2 mg/dL | History of MI and non-fasting TC ≥ 7.2 mg/dL - 115 mmol/L during second and third regimes, major ECI reductions or atypically on plasma or serum osmolality | Placebo 40 mg or placebo | Total CHD, non-fatal MI, any CHD, any stroke | Mean 4.9 years | 70–8% in treatment and 69–7% in control arm at year 5

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**Table 1. Randomized clinical trials of risk and rate of coronary heart disease (CHD) or Stroke.**
### Web Table 2. Randomized clinical trials of ASA and risk of coronary heart disease (CHD), or Stroke.

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Exclusion Criteria</th>
<th>Intervention Groups</th>
<th>Outcome of Interest</th>
<th>Follow-up</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>British Doctors Trial</strong> 1988&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All male doctors resident in UK one half under 40 years of age</td>
<td>Indication or communications for aspirin, history of peptic ulcer, definite stroke or MI</td>
<td>Aspirin: 500 mg ordinary or 300 mg enteric coated per day</td>
<td>Total fatal and non-fatal stroke, any stroke</td>
<td>Minimum 5 years</td>
<td>95% in treatment arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>US Physicians Study 1989</strong></td>
<td>Healthy male physicians 40-79 years of age</td>
<td>Indication or communication for aspirin</td>
<td>Fatal and non-fatal stroke, any stroke</td>
<td>Median 5 years</td>
<td>85% in treatment arm</td>
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<tr>
<td><strong>Thrombosis Prevention Trial 1998</strong></td>
<td>Men between 40 to 69 years of age with CHD referring to 108 practices in UK in the Medical Research Council</td>
<td>A current or recent history of possible peptic ulceration, a history of possible or definite MI or stroke, and other indication incompatible with the clinical trial</td>
<td>Aspirin: 325 mg every other day</td>
<td>Median 5 years</td>
<td>95% in treatment arm</td>
</tr>
</tbody>
</table>

#### Notes:
- **Aspirin:** 100 mg per day
- **Non-aspirin:** N/A

**Compliance:**
- Median 3.5 years
- Median 8.5 years
- Median 8 years
- Median 9.5 years
- Median 10.7 years

#### References:

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### Web Table 3. Randomized controlled trials of ACE inhibitors and risk of coronary heart disease (CHD), or Stroke.

<table>
<thead>
<tr>
<th>Author and year of study (acronym)</th>
<th>Study population</th>
<th>Exclusion criteria</th>
<th>Intervention groups</th>
<th>Outcome of Interest</th>
<th>Follow-up</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DREAM Trial Investigators 2004</strong></td>
<td>Patients 50 years of age or older with impaired fasting plasma glucose levels or impaired glucose tolerance</td>
<td>Indication or communication for ACE inhibitors or diabetes mellitus; history of diabetes, cardiovascular disease or intolerance to ACE inhibitors; or treatment with diuretics, ACE inhibitors, or calcium-channel blockers</td>
<td>Randomized 5 mg per day for the first 2 months, increased to 10 mg per day for 2 months, and increased to 15 mg per day for the second year</td>
<td>Any MI, any stroke</td>
<td>Median 3 years</td>
<td>95.2% in treatment arm and 95.9% in control arm</td>
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<tr>
<td><strong>Liur 1998b</strong></td>
<td>Patients 30 to 59 years old, at least 1 year old, participating in the SOLVD study plane, with systolic BP 160–219 mmHg, and not taking antihypertensive drugs</td>
<td>Baseline BP &lt; 180 mmHg, no history of cardiovascular disease or diabetes, no history of stroke, and not taking antihypertensive or anticoagulant</td>
<td>Nonrandomized 10–20 mg once or twice a day, if not controlled added captopril or hydrochlorothiazide 12.5 mg or 25 mg once or twice a day</td>
<td>Any MI, any stroke</td>
<td>Median 3 years</td>
<td>95.1% in treatment arm and 95.3% in control arm</td>
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<tr>
<td><strong>ADVANCE Collaborative Group 2002</strong></td>
<td>Diabetic patients 40-74 years old, normotensive with DBP &lt;= 80 mmHg, not taking antihypertensive drugs</td>
<td>Age ≤ 65 years, not on antihypertensive drugs</td>
<td>Randomized 15 mg once daily</td>
<td>Any MI, any stroke</td>
<td>Median 4 years</td>
<td>75% in treatment arm and 74.9% in control arm</td>
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<tr>
<td><strong>Safar 2002</strong></td>
<td>Diabetes patients 40-74 years old, normotensive with DBP ≤ 80 mmHg, not taking antihypertensive drugs</td>
<td>Baseline BP ≥ 140 mmHg, no history of cardiovascular disease or diabetes, no history of stroke, and not taking antihypertensive or anticoagulant</td>
<td>Randomized 25 mg once daily</td>
<td>Any MI, any stroke</td>
<td>Median 4 years</td>
<td>70% in treatment arm and 52.7% in control arm</td>
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<tr>
<td><strong>SCAF 2000</strong></td>
<td>Patients 40–74 years, with coronary artery disease, not on angiotensin-converting enzyme inhibitor treatment, blood pressure ≥ 160 mmHg, and not taking antihypertensive drugs</td>
<td>Median 2.5 mg twice daily</td>
<td>Randomized 50 mg once daily</td>
<td>Any MI, any stroke, non-fatal stroke, any stroke</td>
<td>Median 3 years</td>
<td>94% in treatment arm and 86% in control arm</td>
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<tr>
<td><strong>Wang 2005</strong></td>
<td>All patients 80 years old, with systolic BP ≥ 160 mmHg and two or more causes of heart disease (other than diabetes mellitus)</td>
<td>Age ≥ 80 years, not on antihypertensive drugs</td>
<td>Randomized 50 mg once daily</td>
<td>Any MI, any stroke</td>
<td>Median 5 years</td>
<td>95.3% in treatment arm and 95.9% in control arm</td>
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<tr>
<td><strong>Hannam 1999</strong></td>
<td>Patients 30–65 years old, with systolic BP ≥ 140 mmHg and two or more vascular risk factors</td>
<td>Any medical condition, with or without cardiac catheterization, atorvastatin or pravastatin</td>
<td>Randomized 10 mg once daily</td>
<td>Any MI, any stroke</td>
<td>Median 6.5 years</td>
<td>-</td>
</tr>
</tbody>
</table>

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#### References:
Web Table 4. Randomized clinical trials of thalidomide and risk of coronary heart disease (CHD), or Stroke

<table>
<thead>
<tr>
<th>Author and year (study acronym)</th>
<th>Study population</th>
<th>Inclusion criteria</th>
<th>Outcome of interest</th>
<th>Follow-up</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIDP 1979</strong></td>
<td>Hypertensive individuals from 30-69 year old who referred to 14 centers based on resident areas and one center based on employment</td>
<td>Bloodstream and intramuscularly injected</td>
<td>Stepped Care (SC) response increase in medication in special centers: 1. chlorothalidone (25-50mg/day) 2. -resistant 4. hydrochlorothiazide 4- 5 other</td>
<td>Framed CHD, final stroke</td>
<td>Maximum 5 years</td>
</tr>
<tr>
<td><strong>HIDP 1982</strong></td>
<td>Hypertensive individuals from 30-69 year old who referred to 14 centers based on resident areas and one center based on employment</td>
<td>Bloodstream and intramuscularly injected</td>
<td>Stepped Care (SC) response increase in medication in special centers: 1. chlorothalidone (25-50mg/day) 2. -resistant 4. hydrochlorothiazide 4- 5 other</td>
<td>Framed CHD, final stroke, non-fatal stroke, non-fatal MI</td>
<td>Maximum 5 years</td>
</tr>
<tr>
<td><strong>SHEP 1991</strong></td>
<td>Patients 60 years and above referred by mass media and community screening sources</td>
<td>Bloodstream and intramuscularly injected</td>
<td>Stepped Care (SC) response increase in medication in special centers: 1. chlorothalidone (25-50mg/day) 2. -resistant 4. hydrochlorothiazide 4- 5 other</td>
<td>Framed CHD, final CHD, any stroke, non-fatal MI</td>
<td>Maximum 5 years</td>
</tr>
<tr>
<td><strong>SHEP 1995</strong></td>
<td>Patients 60 years and above referring to 5 clinical centers in the US, with unscreened essential hypertension, systolic blood pressure (SBP) ≥ 160 for SBP &gt; ≤ 180 and SBP &gt; ≤ 190 for patients who were referred for drug withdrawal before intervention</td>
<td>Bloodstream and intramuscularly injected</td>
<td>Stepped Care (SC) response increase in medication in special centers: 1. chlorothalidone (25-50mg/day) 2. -resistant 4. hydrochlorothiazide 4- 5 other</td>
<td>Framed CHD, any stroke, non-fatal MI</td>
<td>Maximum 5 years</td>
</tr>
<tr>
<td><strong>Amery 1989</strong></td>
<td>All elderly patients referring to the outpatient clinic: 1 age ≥ 60 years 2 SBP &gt; ≤ 160-180 mmHg and DBP &gt; ≤ 90-109 mmHg, 40 years old or older</td>
<td>Bloodstream and intramuscularly injected</td>
<td>History and or sign of major cardiovascular diseases and other major diseases</td>
<td>Framed CHD, any stroke, non-fatal MI</td>
<td>Maximum 5 years</td>
</tr>
<tr>
<td><strong>Australian Therapeutic Trial 1980</strong></td>
<td>Australian or European volunteers who had SBP &gt; ≤ 160-180 mmHg and DBP &gt; ≤ 90-109 mmHg, or those with diabetes or ECG abnormality in the previous year</td>
<td>Bloodstream and intramuscularly injected</td>
<td>Stepped Care (SC) response increase in medication in special centers: 1. chlorothalidone (25-50mg/day) 2. -resistant 4. hydrochlorothiazide 4- 5 other</td>
<td>Framed CHD, any stroke, non-fatal MI</td>
<td>Maximum 5 years</td>
</tr>
<tr>
<td><strong>Holford 1989</strong></td>
<td>Persons screened in 14 centers; aged 35-60 years of age and 7% between 20-39 years of age were recruited and screened; age between 20-40 years; SBP &gt; ≤ 180 mmHg and DBP &gt; ≤ 100 mmHg 2 sessions</td>
<td>Bloodstream and intramuscularly injected</td>
<td>Nicotine or aspirin secondary hyperlipidemia, with or without antihypertensive drugs medication for angiopathy, had a history of MI or stroke, while the prevalence of the underlying conditions, but required renal functions, more diuretics, had serious, any serious intercurrent disease, including malignancy to be present at the time of examination, or had a serum potassium concentration of 3.7 mmol/L or less</td>
<td>Framed CHD, any stroke, non-fatal MI</td>
<td>Maximum 5 years</td>
</tr>
<tr>
<td><strong>McKenna screening party 1982</strong></td>
<td>The age-sex registers of 225 group practices throughout England, Scotland, and Wales attended by written invitations and women 65-74 year old with SBP &gt; ≤ 160-180 mmHg and DBP &gt; ≤ 115 mmHg</td>
<td>Bloodstream and intramuscularly injected</td>
<td>Subjects with known or suspected secondary hyperlipidemia, with or without antihypertensive drugs medication for angiopathy, had a history of MI or stroke, while the prevalence of the underlying conditions, but required renal functions, more diuretics, had serious, any serious intercurrent disease, including malignancy to be present at the time of examination, or had a serum potassium concentration of 3.7 mmol/L or less</td>
<td>Framed CHD, any stroke, non-fatal MI</td>
<td>Maximum 5 years</td>
</tr>
<tr>
<td><strong>Sainsbury 1987</strong></td>
<td>Patients screened in 196 centers in 25 counties in women and eastern Europe — 60 years old, with SBP &gt; ≤ 160-180 mmHg, standing SBP &gt; ≤ 145 mmHg, DBP &gt; ≤ 90mmhg, or those with diabetes or ECG abnormality in the previous year</td>
<td>Bloodstream and intramuscularly injected</td>
<td>Subjects with known or suspected secondary hyperlipidemia, with or without antihypertensive drugs medication for angiopathy, had a history of MI or stroke, while the prevalence of the underlying conditions, but required renal functions, more diuretics, had serious, any serious intercurrent disease, including malignancy to be present at the time of examination, or had a serum potassium concentration of 3.7 mmol/L or less</td>
<td>Framed CHD, any stroke, non-fatal MI</td>
<td>Maximum 5 years</td>
</tr>
<tr>
<td><strong>Liu 1999</strong></td>
<td>Patient registration or population screening to 51 clinical trials</td>
<td>Bloodstream and intramuscularly injected</td>
<td>Subjects with known or suspected secondary hyperlipidemia, with or without antihypertensive drugs medication for angiopathy, had a history of MI or stroke, while the prevalence of the underlying conditions, but required renal functions, more diuretics, had serious, any serious intercurrent disease, including malignancy to be present at the time of examination, or had a serum potassium concentration of 3.7 mmol/L or less</td>
<td>Framed CHD, any stroke, non-fatal MI</td>
<td>Maximum 5 years</td>
</tr>
<tr>
<td><strong>Davila 1990</strong></td>
<td>Patients referring to 116 health centers throughout Sweden and women who were screened to attend an informative session, were referred to the study</td>
<td>Bloodstream and intramuscularly injected</td>
<td>Subjects with known or suspected secondary hyperlipidemia, with or without antihypertensive drugs medication for angiopathy, had a history of MI or stroke, while the prevalence of the underlying conditions, but required renal functions, more diuretics, had serious, any serious intercurrent disease, including malignancy to be present at the time of examination, or had a serum potassium concentration of 3.7 mmol/L or less</td>
<td>Framed CHD, any stroke, non-fatal MI</td>
<td>Maximum 5 years</td>
</tr>
<tr>
<td><strong>Coper 1988</strong></td>
<td>At least 35-year-old men and women aged 40-80 year old with SBP &gt; ≤ 170 mmHg (50%) or those with diabetes or ECG abnormality in the previous year</td>
<td>Bloodstream and intramuscularly injected</td>
<td>Subjects with known or suspected secondary hyperlipidemia, with or without antihypertensive drugs medication for angiopathy, had a history of MI or stroke, while the prevalence of the underlying conditions, but required renal functions, more diuretics, had serious, any serious intercurrent disease, including malignancy to be present at the time of examination, or had a serum potassium concentration of 3.7 mmol/L or less</td>
<td>Framed CHD, any stroke, non-fatal MI</td>
<td>Maximum 5 years</td>
</tr>
<tr>
<td><strong>Vaccarino 1979</strong></td>
<td>Men (majority with mild to moderate hypertension), aged 40-80 year old, DSB &gt; ≤ 100 mmHg of patients with high blood pressure, including mild hypertension</td>
<td>Bloodstream and intramuscularly injected</td>
<td>Subjects with known or suspected secondary hyperlipidemia, with or without antihypertensive drugs medication for angiopathy, had a history of MI or stroke, while the prevalence of the underlying conditions, but required renal functions, more diuretics, had serious, any serious intercurrent disease, including malignancy to be present at the time of examination, or had a serum potassium concentration of 3.7 mmol/L or less</td>
<td>Framed CHD, any stroke, non-fatal MI</td>
<td>Maximum 5 years</td>
</tr>
<tr>
<td><strong>Medical Research Council 1988</strong></td>
<td>Men and women screened in 11 centers; aged 65 years old, DSB &gt; ≤ 100 mmHg of patients with high blood pressure, including mild hypertension</td>
<td>Bloodstream and intramuscularly injected</td>
<td>Subjects with known or suspected secondary hyperlipidemia, with or without antihypertensive drugs medication for angiopathy, had a history of MI or stroke, while the prevalence of the underlying conditions, but required renal functions, more diuretics, had serious, any serious intercurrent disease, including malignancy to be present at the time of examination, or had a serum potassium concentration of 3.7 mmol/L or less</td>
<td>Framed CHD, any stroke, non-fatal MI</td>
<td>Maximum 5 years</td>
</tr>
</tbody>
</table>

a) Five-year findings of the hypertension detection and follow-up program. | b) Five-year findings of the hypertension detection and follow-up program. | c) Cohort studies of all selected hypertensive patients. | d) Five-year findings of the hypertension detection and follow-up program. | e) Five-year findings of the hypertension detection and follow-up program. | f) Five-year findings of the hypertension detection and follow-up program. | g) Cohort studies of all selected hypertensive patients. | h) Cohort studies of all selected hypertensive patients. | i) Five-year findings of the hypertension detection and follow-up program. | j) Cohort studies of all selected hypertensive patients. | k) Five-year findings of the hypertension detection and follow-up program. | l) Cohort studies of all selected hypertensive patients. | m) Cohort studies of all selected hypertensive patients. | n) Cohort studies of all selected hypertensive patients. | o) Cohort studies of all selected hypertensive patients. | p) Cohort studies of all selected hypertensive patients. | q) Cohort studies of all selected hypertensive patients. | r) Cohort studies of all selected hypertensive patients. | s) Cohort studies of all selected hypertensive patients. | t) Cohort studies of all selected hypertensive patients. | u) Cohort studies of all selected hypertensive patients. | v) Cohort studies of all selected hypertensive patients. | w) Cohort studies of all selected hypertensive patients. | x) Cohort studies of all selected hypertensive patients. | y) Cohort studies of all selected hypertensive patients. | z) Cohort studies of all selected hypertensive patients. |