Meta-Analysis

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

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Cite this article as: Sepanlou SG, Farzadfar F, Jafari E, Danaei G. Cardiovascular disease prevention using fixed dose pharmacotherapy in Iran: updated meta-analyses and mortality estimation. *Arch Iran Med*. 2012; **15(9):** 531 – 537.

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 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.[1,2] 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.[5–8] Considering the high levels of exposure to these risk factors in many developing countries,[9,10] 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.

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Accepted for publication: 20 June 2012

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 JUPITER[17] and Women's Health Study[18]) 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[19] and by Antithrombotic Trialists' Collaboration for aspirin in 2002.[20] For statins, we included the trials identified in a recently conducted systematic review by one of the authors.[21]

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 of antihypertensives in which the dose of the agent was not within the standard range recommended by the Joint National Committee.[22]

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.[23] We used the Egger's test to evaluate publication bias[24] 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.[22]

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:

$$\textit{Multiplicative joint RR} = \prod_{i=1}^{n} RR_i$$

$$\textit{Additive joint RR} = 1/(\sum_{i=1}^{n}(\frac{1}{RR_i} - 1) + 1)$$

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.[14]). 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.[14,19,25] 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[26] 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-

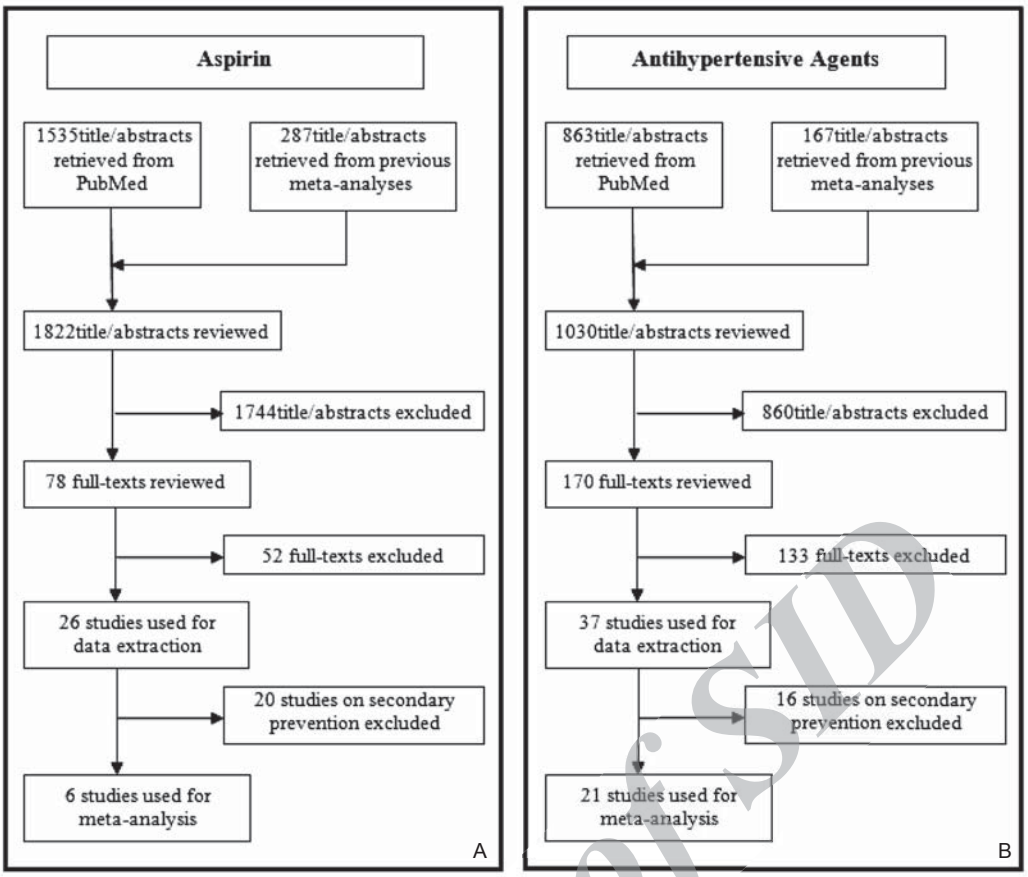

Figure 1. Flowcharts for systematic reviews of aspirin (A) and anti-hypertensive agents (B)

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] Finally to estimate number of preventable deaths we multiplied them by total mortality due to IHD and stroke:

Preventable deaths = joint RR * 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 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

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

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

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

Polypill Components	Outcome	Multiplicative RRs	Additive RRs
An ACE-inhibitor in full dose, aspirin, and a statin	IHD	0.47 (0.37, 0.61)	0.54 (0.45, 0.64)
	Stroke	0.68 (0.52, 0.90)	0.70 (0.57, 0.87)
A thiazide in full dose, aspirin, and a statin	IHD	0.48 (0.36, 0.63)	0.54 (0.44, 0.65)
	Stroke	0.48 (0.36, 0.59)	0.51 (0.44, 0.60)
An ACE-inhibitor in half dose, a thiazide in half dose, aspirin, a statin	IHD	0.49 (0.38, 0.63)	0.54 (0.45, 0.65)
	Stroke	0.57 (0.44, 0.74)	0.61 (0.51, 0.73)
An ACE-inhibitor in half dose, a thiazide in half dose, and a statin	IHD	0.60 (0.51, 0.70)	0.63 (0.54, 0.72)
	Stroke	0.58 (0.47, 0.71)	0.62 (0.53, 0.72)

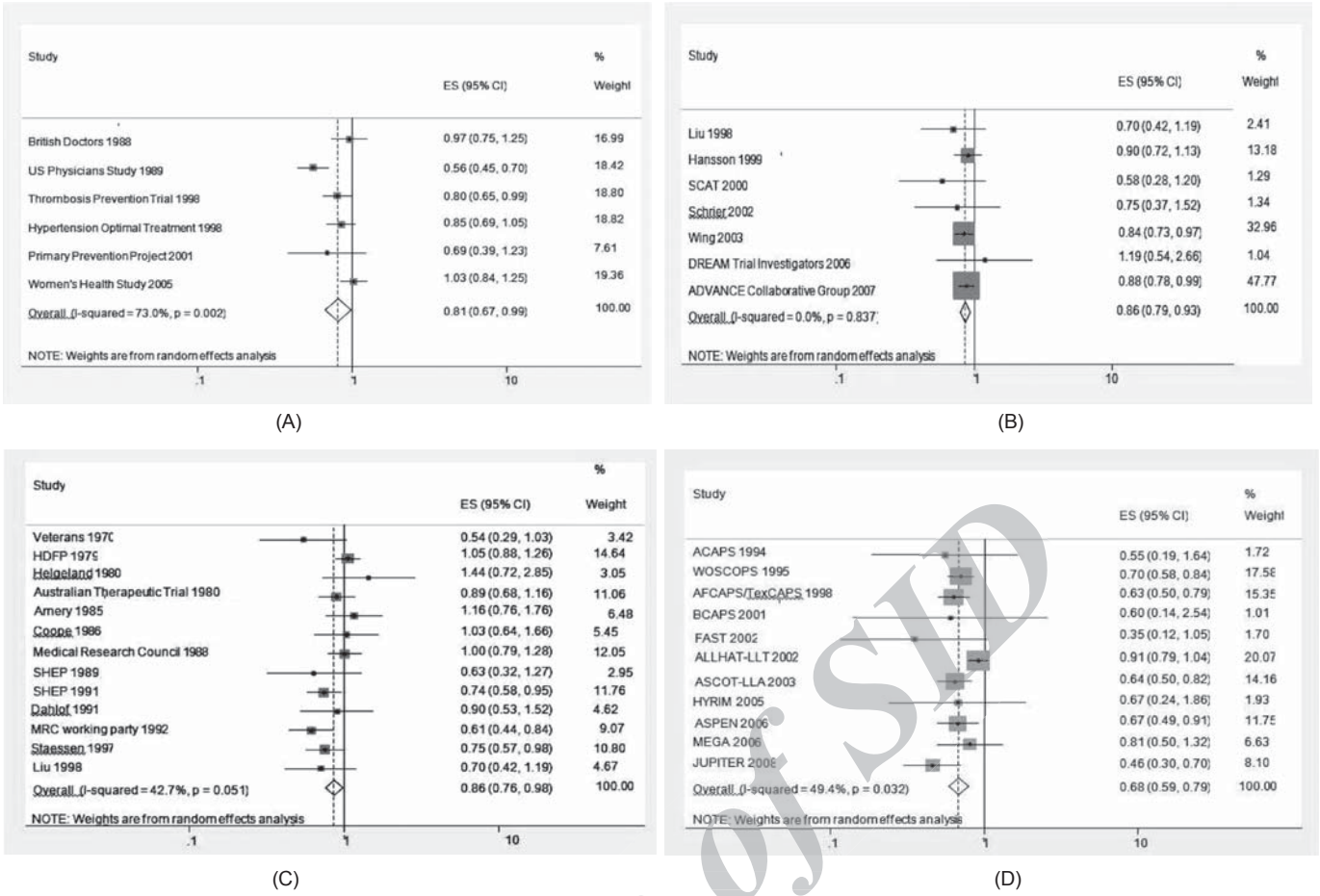

Figure 2. Pooled relative risks of mortality from ischemic heart disease. **A)** Aspirin **B)** ACE-inhibitors **C)** Thiazides **D)** Statins

statin trials had reported RRs by age and sex and only 2 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 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

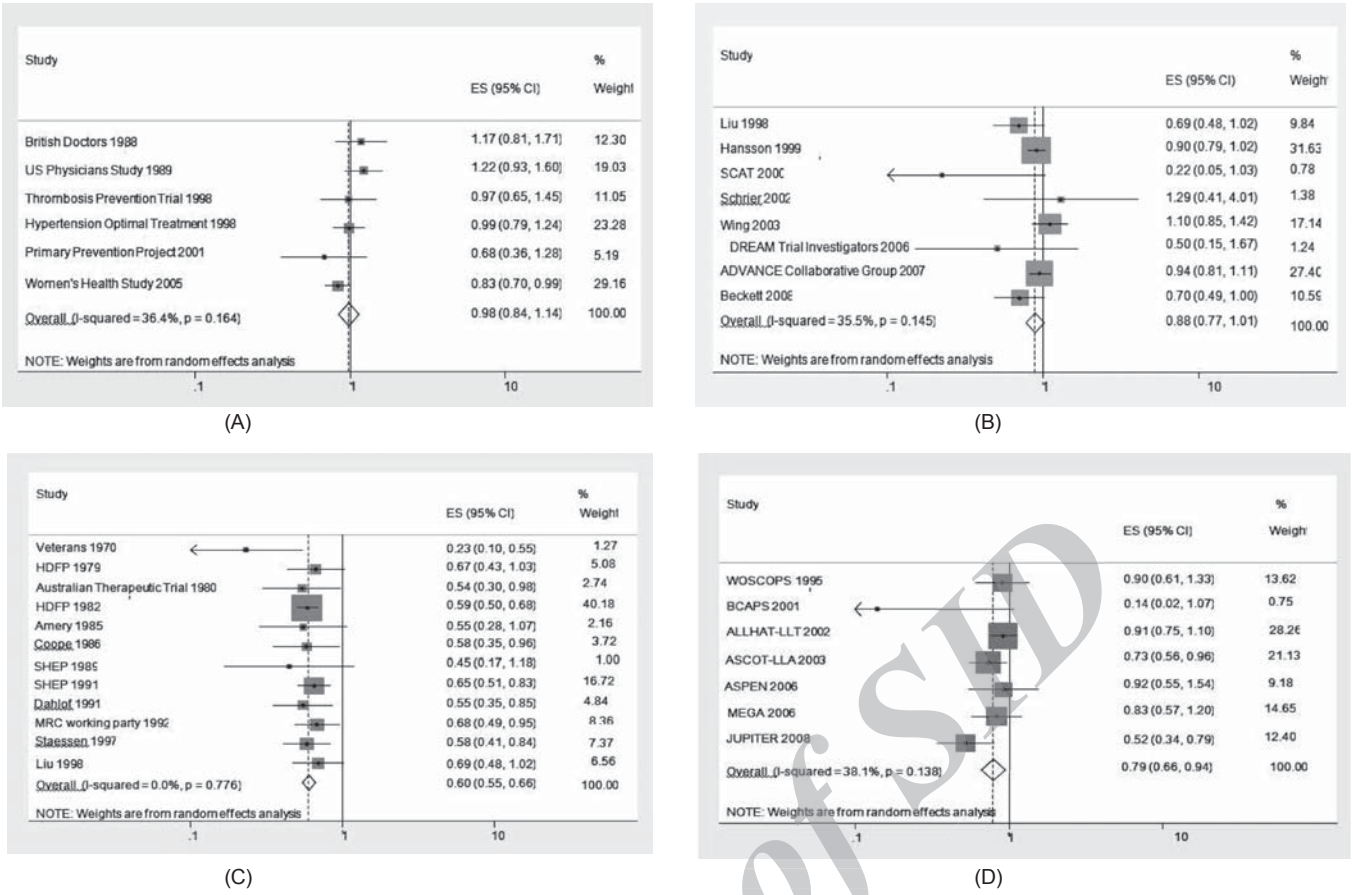

Figure 3. Pooled relative risks of mortality from stroke. **A)** Aspirin **B)** ACE-inhibitors **C)** Thiazides **D)** Statins

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,[29] which has been questioned in more recent randomized trials[30] 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.[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

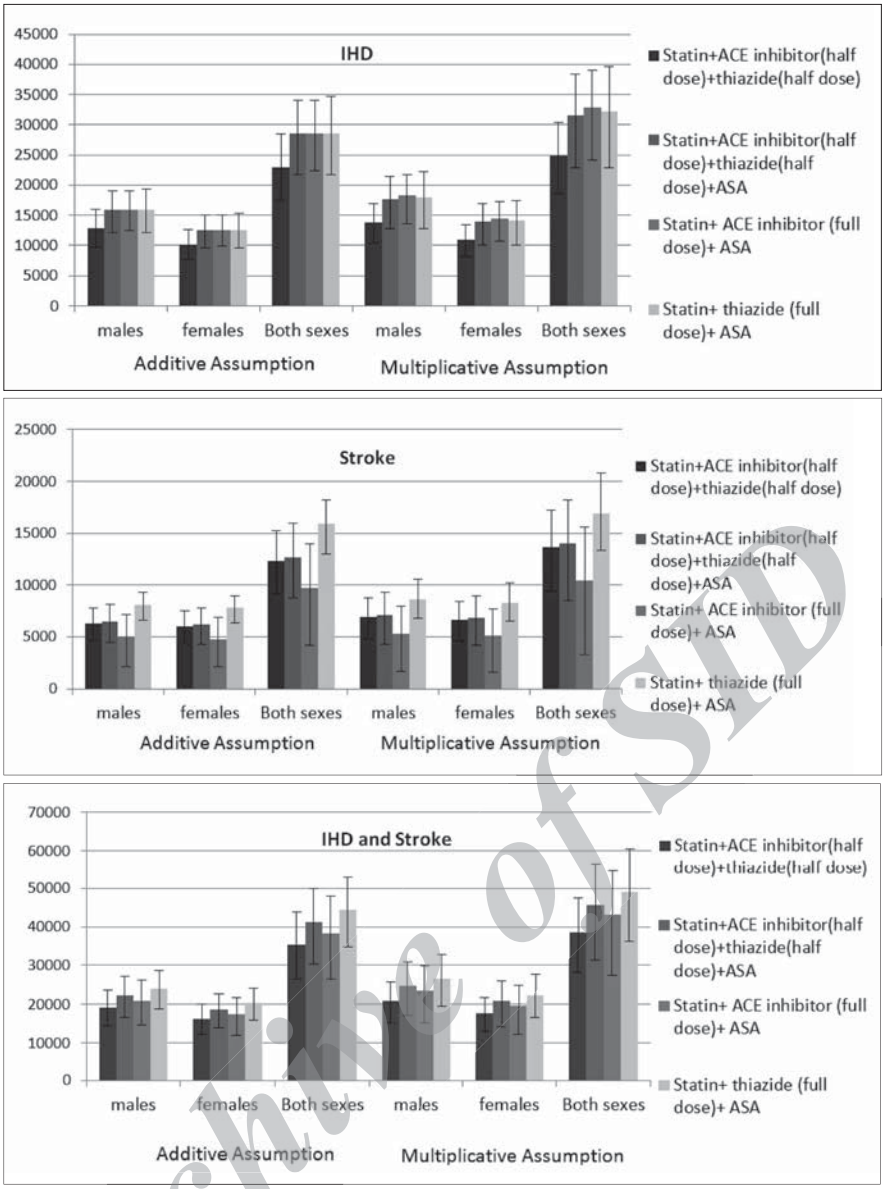

Figure 4. The number of preventable deaths and their 95% uncertainty intervals. ACE: Angiotensin Coverting Enzyme; ASA: Acetyl Salicilic Acid

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 competeing 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).[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 manufactured 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

1. Global status report on noncommunicable diseases 2010. World Health Organization. Geneva: 2011.
2. Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJ, et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med. 2009; **6(4):** 1000058.
3. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. *J Am Coll Cardiol*. 2007; **50(22):** 2128 – 2132.
4. Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970 – 2002. *JAMA*. 2005; **294(10):** 1255 – 1259.
5. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980 – 2000. *N Engl J Med*. 2007; **356(23):** 2388 – 2398.
6. Goldman L, Phillips KA, Coxson P, Goldman PA, Williams L, Hunink MG, et al. The effect of risk factor reductions between 1981 and 1990 on coronary heart disease incidence, prevalence, mortality and cost. *J Am Coll Cardiol*. 2001; **38(4):** 1012 – 1017.
7. Young F, Capewell S, Ford ES, Critchley JA. Coronary mortality declines in the U.S. between 1980 and 2000 quantifying the contributions from primary and secondary prevention. *Am J Prev Med*. 2010; **39(3):** 228 – 234.
8. Capewell S, Hayes DK, Ford ES, Critchley JA, Croft JB, Greenlund KJ, et al. Life-years gained among US adults from modern treatments and changes in the prevalence of 6 coronary heart disease risk factors between 1980 and 2000. *Am J Epidemiol*. 2009; **170(2):** 229 – 236.
9. Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. *Lancet*. 2011; **377(9765):** 578 – 586.
10. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, et al. National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. *Lancet*. 2011; **377(9765):** 568 – 577.
11. World Health Organization. Secondary Prevention of Noncommunicable Diseases in Low and Middle Income Countries Through Community-based and Health Service Intervention. Wellcome Trust meeting report 1 – 3 August. *World Health Organization*. Geneva: 2001.
12. The World Health Report 2002. Reducing risks, promoting healthy life. *World Health Organization*.Geneva: 2002.
13. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ*. 2003; **326(7404):**1419.
14. Malekzadeh F, Marshall T, Pourshams A, Gharravi M, Aslani A, Nateghi A, et al. A pilot double-blind randomised placebo-controlled trial of the effects of fixed-dose combination therapy ('polypill') on cardiovascular risk factors. *Int J Clin Pract*. 2010; **64(9):** 1220 – 1227.
15. Rodgers A, Patel A, Berwanger O, Bots M, Grimm R, Grobbee DE, et al. An international randomised placebo-controlled trial of a four-component combination pill ("polypill") in people with raised cardiovascular risk. *PLoS One*. 2011; **6(5):**19857.
16. Yusuf S, Pais P, Afzal R, Xavier D, Teo K, Eikelboom J, et al. 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(9672):** 1341 – 1351.
17. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, et al.Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008; **359(21):**2195 – 2207.
18. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005; **352(13):**1293 – 1304.
19. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009; **338:** 1665.
20. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002; **324(7329):** 71 – 86.
21. Danaei G, Tavakkoli M, Hernan MA, Bias in observational studies of prevalent users: lessons for comparative effectiveness research from a meta-analysis of statins. *Am J Epidemiol*. 2012; **175(4):**250 – 262.
22. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *National Institutes of Health*. 2004.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; **7(3):** 177 – 188.
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; **315(7109):**629 – 634.
25. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ*. 2003; **326(7404):**1427.
26. Harris RJ, Bradburn MJ, Deeks JJ, Harbord RM, Altman DG, Sterne JAC. Metan: fixed- and random-effects meta-analysis. *Stata J*. 2008; **8(1):** 3 – 28.
27. Khosravi A, Taylor R, Naghavi M, Lopez AD. Mortality in the Islamic Republic of Iran, 1964 – 2004. *Bull World Health Organ*. 2007; **85(8):**607 – 614.
28. Farzadfar F, Danaei G, Namdaritabar H, Rajaratnam JK, Marcus JR, Khosravi A, et al. National and subnational mortality effects of metabolic risk factors and smoking in Iran: a comparative risk assessment. *Popul Health Metr*. 2011;**9(1):**55.
29. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ*. 2002; **325(7374):**1202.
30. Antoniades C, Antonopoulos AS, Tousoulis D, Marinou K, Stefanadis C. Homocysteine and coronary atherosclerosis: from folate fortification to the recent clinical trials. *Eur HeartJ*. 2009; **30(1):** 6 – 15.
31. Tolman KG. The liver and lovastatin. *Am J Cardiol*. 2002; **89(12):** 1374 – 1380.
32. Bader T. The myth of statin-induced hepatotoxicity. *Am J Gastroenterol*. 2010; **105(5):** 978 – 980.
33. Mora S, Glynn RJ, Hsia J, MacFadyen JG, Genest J, Ridker PM. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. *Circulation*. 2010; **121(9):** 1069 – 1077.
34. Floyd JS, Heckbert SR, Weiss NS, Carrell DS, Psaty BM. Use of administrative data to estimate the incidence of statin-related rhabdomyolysis. *JAMA*. 2012; **307(15):**1580 – 1582.
35. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA*. 2003; **289(13):** 1681 – 1690.
36. Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011; **305(24):**2556 – 2564.
37. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010; **375(9716):** 735 – 742.
38. van Gils PF, Over EA, Hamberg-van Reenen HH, de Wit GA, van den Berg M, Schuit AJ, et al. The polypill in the primary prevention of cardiovascular disease: cost-effectiveness in the Dutch population. *BMJ Open*. 2011; **1(2):** e000363.
39. Gaziano TA, Opie LH, Weinstein MC. Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. *Lancet*. 2006; **368(9536):**679 – 686.
40. Lim SS, Gaziano TA, Gakidou E, Reddy KS, Farzadfar F, Lozano R, et al. Prevention of cardiovascular disease in high-risk individuals in low-income and middle-income countries: health effects and costs. *Lancet.* 2007; **370(9604):**2054 – 2062.

Web Table 1. Randomized clinical trials of statins and risk of coronary heart disease (CHD) or Stroke.

Author and year (study acronym)	Study population	Exclusion criteria	Intervention groups	Outcome of interest	Follow-up	Compliance
Furberg 1994 (ACAPS)[a]	919 asymptomatic men and women, 40 to 79 years old, with early carotid atherosclerosis as defined by B-mode ultrasonography and LDL cholesterol between the 60th and 90th percentiles, mean age 61.7 years and 51.5% male	History of MI, stroke, or angina	Lovastatin 20–40 mg/d or placebo	Non-fatal MI, any CHD	Mean 2.84 years	77% in both arms
Downs 1998 (AFCAPS/TexCAPS)[b]	5608 men and 997 women 45 to 73 years old with average TC and LDL-C and below-average HDL-C and had no prior history, signs, or symptoms of definite myocardial infarction, angina, claudication, CVA, or TIA	Uncontrolled HTN, secondary hyperlipidemia, or type 1 or type 2 DM that was either managed with insulin or associated with a glycohemoglobin>10%. a body weight of more than 50% greater than the desirable limit for height	Lovastatin (20–40 mg/d) or placebo in addition to a low–saturated fat, low-cholesterol diet	Any CHD	Mean 5.2 years	71% in treatment arm and 63% in controls
ALLHAT-LLT 2002[c]	Ambulatory persons (n=10355), aged 55 years or older, with LDL of 120 to 189 mg/dL (100 to 129 mg/dL if known CHD) and triglycerides lower than 350 mg/dL, mean age 66 years, 49% women, 38% black and 23% Hispanic, 14% had a history of CHD, and 35% had type 2 diabetes	Currently receiving lipid-lowering therapy, taking large doses of niacin, or taking Probucol in the last year; known to be intolerant of statins or to have significant liver or kidney disease (serum ALT >100 IU/L or serum creatinine>2.0 mg/dL or other contraindications for statin therapy; or had a known secondary cause of hyperlipidemia	Pravastatin 40 mg/d or usual care	Fatal and non-fatal CHD, any CHD, fatal and non-fatal stroke, any stroke	Mean 4.8 years	71% in the control arm, 77% in treatment arm
Sever 2003 (ASCOT-LLA)[d]	19342 hypertensive patients (aged 40–79 years with at least three other CVD risk factors and fasting TC<6.5 mmol/L mainly white (95%) and male (81%), with a mean age of 63 years and at least 3 of the following: LVH, abnormalities on ECG, DM, PAD, previous stroke or TIA, male, aged 55 or older, microalbuminuria or proteinuria, smoking, cholesterol/HDL ≥ 6 or family history of premature CHD	Previous MI, current treated angina, CVD in the past 3 months, fasting TG> 4.5 mmol/L, CHF, uncontrolled arrhythmia or any other clinically important hematological or biochemical abnormality on screening	Atorvastatin 10 mg/d or placebo	Any CHD, any stroke	Median 3.3 years	87% in treatment and 91% in control after 3 years
Knopp 2006 (ASPEN)[e]	2411 patients with type 2 DM for 3 years or more and low LDL (<3.6 mmol/L if history of MI or interventional procedure and < 4.1 mmol/L if not), TG<600 mg/dL, aged 40-75	Type 1 DM, MI, interventional procedure or episodes of unstable angina less than 3 months before screening, HbA1c>10%, active liver disease or hepatic dysfunction, severe renal disease, CHF treated with digoxin, CK>3 times upper limit, BP>160/100 mmHg, BMI >35 kg/m2, alcohol or drug abuse, hypersensitivity to study medication, current or planned pregnancy, placebo run-in compliance <80%, use of excluded medications	Atorvastatin 10 mg/d or placebo	Any MI, any stroke	Median 4 years	67.5% in treatment arm and 57.6% in controls
Hedblad 2001 (BCAPS)[f]	793 men and women 49 to 70 years of age with plaque in the right carotid artery but with no symptoms of CAD, mean age 61.8, 41.5% male	History of MI, angina pectoris, or stroke within the preceding 3 months; history of surgical intervention in the right carotid artery; regular use of beta-blockers or statins; SBP>160 or DBP>95 mmHg; TC>8.0 mmol/L; hyperglycemia suspected to require insulin treatment; and conditions that in the opinion of the investigator rendered the subject unsuitable for the trial	Fluvastatin 40 mg/d or placebo	Any MI, any stroke	Mean 3 years	79% in treatment and 77% in placebo arm
Sawayama 2002 (FAST)[g]	246 patients with TC ≥ 220 mg/dL aged 30–89, mean age 66.1 yrs and 31.3% male	TG ≥ 350 mg/dL, uncontrolled heart failure, recent (<6 months) MI; severe or unstable angina pectoris; hypothyroidism/hyperthyroidism or other endocrine diseases; secondary hyperlipidemia; uncontrolled DM; uncontrolled HTN; heavy drinking; obese patients on weight reduction programs; diseases that might interfere with drug absorption; any severe illness; and treatment with certain drugs, including corticosteroids, other lipid-lowering agents or antacids containing aluminum salts	Pravastatin 10 mg/d or diet alone	Fatal MI, non-fatal MI, any CHD	2 years	-
Anderssen 2005 (HYRIM)[h]	568 drug-treated hypertensive men aged 40–74 years with TC 4.5–8.0 mmol/L, TG < 4.5 mmol/L, BMI 25–35 kg/m2, and a sedentary lifestyle	Any symptomatic CVD (MI, angina pectoris, stroke), CHF, type 1 DM, history of coronary intervention, need for treatment with lipid-lowering medications other than the study drug, known or suspected impaired hepatic or renal function or malignancy, history of alcohol and/or drug abuse, vegetarian diet or diet comprising a high omega-3 fatty acid intake, and inability to perform physical exercise	Fluvastatin 40 mg/d or lifestyle in a 2 by 2 factorial design	Any CHD	4 years	-
Ridker 2008 (JUPITER)[i]	17802 patients including men over 50 and women over 60 without history of CVD and LDL<130 mg/dL and CRP > 2 mg/L and triglycerides < 500 mg/dL	Patients with previous or current use of lipid-lowering therapy, or postmenopausal HRT, evidence of hepatic dysfunction, high CK level, high creatinine level, DM, uncontrolled HTN, cancer within 5 years before enrollment, uncontrolled hypothyroidism, and a recent history of alcohol or drug abuse or another medical condition that might compromise safety or the successful completion of the study	Rosuvastatin, 20 mg/d or matching placebo	Non-fatal MI, any MI, non-fatal stroke, any stroke	Maximum 5 years; median 1.9 years	75% in both arms
Nakamura 2006 (MEGA)[j]	7,832 hypercholesterolemic patients (total cholesterol 5.69 to 6.98 mmol/L) and no history of CHD, men and post-menopausal women aged 40–70	Familial hypercholesterolemia, history of angina, MI or bypass surgery or PCI, ECG abnormalities consistent with MI, history of PAD, stroke or TIA, congenital or rheumatic heart disease, chronic atrial fibrillation, current diagnosis of malignancy, severe liver or kidney disease, poorly controlled HTN or DM, secondary hyperlipidemia, current use of corticosteroids and other conditions at the discretion of the individual physician	Pravastatin 10-20 mg/d and diet vs diet alone	Fatal MI, non-fatal MI, any MI, any stroke	Mean 5.3 years	89% in treatment arm
Shepherd 1995 (WOSCOPS)[k]	6595 men, 45 to 64 years of age, with a mean plasma TC of 272 mg/dL	History of MI and non-fasting TC < 252 mg/dL, LDL < 155 mg/dL during second and third visits, major ECG abnormalities or arrhythmias or serious illness	Pravastatin 40 mg/d or placebo	Fatal CHD, non-fatal MI, any CHD, any stroke	Mean 4.9 years	70.4% in treatment and 69.2% in controls at year 5

a) Furberg CD, Adams HP, Jr., Applegate WB, Byington RP, Espeland MA, Hartwell T, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. *Circulation*. 1994; **90:** 1679 – 1687.
b) Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998; **279:** 1615 – 1622.
c) Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*. 2002; **288:** 2998 – 3007.
d) Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003; **361:** 1149 – 1158.
e) Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care*. 2006; **29:** 1478 – 1485.
f) Hedblad B, Wikstrand J, Janzon L, Wedel H, Berglund G. Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: Main results from the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). *Circulation*. 2001; **103:** 1721 – 1726.
g) Sawayama Y, Shimizu C, Maeda N, Tatsukawa M, Kinukawa N, Koyanagi S, et al. Effects of probucol and pravastatin on common carotid atherosclerosis in patients with asymptomatic hypercholesterolemia. Fukuoka Atherosclerosis Trial (FAST). *J Am Coll Cardiol*. 2002; **39:** 610 – 616.
h) Anderssen SA, Hjelstuen AK, Hjermann I, Bjerkan K, Holme I. Fluvastatin and lifestyle modification for reduction of carotid intima-media thickness and left ventricular mass progression in drug-treated hypertensives (HYRIM). *Atherosclerosis*. 2005; **178:** 387 – 397.
i) Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein (JUPITER). *N Engl J Med*. 2008; **359:** 2195-2207.
j) Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet*. 2006; **368**: 1155 – 1163.
k) Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group (WOSCOPS). *N Engl J Med*. 1995; **333:** 1301 – 1307.

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

Author and year (study acronym)	Study population	Exclusion criteria	Intervention groups	Outcome of interest	Follow-up	Compliance
British Doctors 1988[a]	All male doctors resident in UK one half under 60 years of age	Indication or contraindication for aspirin, history of peptic ulcer, definite stroke or MI	Aspirin: 500 mg ordinary or 300 mg enteric coated per day	Fatal MI, non-fatal MI, any CHD, fatal stroke, non-fatal stroke, any stroke	Maximum 6 years	70% in treatment arm
US Physicians Study 1989[b]	Healthy male physicians 40 to 80 years of age	Indication or contraindication for aspirin	Aspirin: 325 mg every other day	Fatal MI, non-fatal MI, any CHD, fatal stroke, Non-fatal stroke, any stroke	Median 5 years	
Thrombosis Prevention Trial 1998[c]	Men between 45 to 69 years of age at risk of CHD referring to 108 practices in UK in the Medical Research Council	A current or recent history of possible peptic ulceration; a history of possible or definite MI or stroke; and other medication incompatible with trial treatment	Aspirin: 75 mg per day	Fatal MI, non-fatal MI, any CHD, fatal stroke, Non-fatal stroke, any stroke	Median 5 years	98% in treatment arm and 100% in control arm
Hypertension Optimal Treatment 1998[d]	Patients recruited from 26 countries in Europe, North and South America, and Asia, aged 50–80 years (mean 61·5 years) with hypertension and diastolic blood pressure between 100 mm Hg and 115 mm Hg (mean 105 mm Hg)	Not discretely mentioned	Aspirin (75 mg per day) + antihypertensive	Any MI, any stroke	Median 3.8 years	
Primary Prevention Project 2001[e]	Old age (65 years); hypertension (SBP 160 mm Hg or DBP 95 mm Hg on at least three separate occasions); hypercholesterolaemia (TC>6·4 mmol/L on at least two separate occasions); DM (fasting venous plasma glucose concentration > 7·8 mmol/L on at least two separate occasions [chronic drug treatment for any of the three latter conditions was also a criterion for inclusion]); obesity (body mass index (30 kg/m2); and family history of MI before 55 years of age in at least one parent or sibling Participants were screened for eligibility when they attended their general practitioner's (315 GP) surgery for any reason. A small proportion of patients were recruited among hypertensive outpatients attending (15) hospital hypertension units (UK)	Treatment with antiplatelet drugs (history of vascular events or diseases); chronic useof anti-inflammatory agents or anticoagulants; contraindications to aspirin; diseases with predictable poor short-term prognosis; and predictable psychological or logistical difficulties affecting compliance with the trial requirements	Aspirin (100 mg per day) + vitamin E (2×2 factorial design)	Fatal MI, non-fatal MI, any CHD, fatal stroke, non-fatal stroke, any stroke	Median 3.6 years	80% in treatment arm, 86.9% in control arm
Women›s Health Study 2005[f]	Female health professionals invited by letters, 45 years of age or older; no history of CHD, CVD, cancer (except nonmelanoma skin cancer), or other major chronic illness; no history of side effects to any of the study medications; not taking aspirin or NSAIDs more than once a week (or were willing to forego their use during the trial); not taking anticoagulants or corticosteroids; and not taking individual supplements of vitamin A, E, or beta carotene more than once a week.	Unwillingness to participate	Aspirin (100 mg every other day)+vitamin E (2×2 factorial design)	Fatal MI, non-fatal MI, any CHD, fatal stroke, non-fatal stroke, any stroke	Median 10.1 years	

a) Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J (Clin Res Ed)*. 1988; 296: 313 – 316.
b) Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med*. 1989; **321: 129 – 135.**
c) Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet*. 1998; **351:** 233 – 241.
d) Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998; **351:** 1755 – 1762.
e) de Gaetano G. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. *Lancet*. 2001; **357:** 89 – 95.
f) Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005; **352:** 1293 – 1304.

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

Author and year (study acronym)	Study population	Exclusion criteria	Intervention groups	Outcome of interest	Follow-up	Compliance
DREAM Trial Investigators 2006[a]	Patients 30 years of age or older with impaired fasting plasma glucose levels or impaired glucose tolerance	History of diabetes, cardiovascular disease or intolerance to ACE inhibitors or thiazolidinediones	Ramipril 5 mg mg/day for the first 2 months, increased to 10 mg/day from 2 months to 1 year, and increased to 15 mg/day for the second year	Any MI, any stroke	Median 3 years	82.6% in treatment arm and 82.3% in control arm
Liu 1998[b]	Patients at least 60 years of age, consenting to participate, sitting SBP 160–219 mmHg averaged at 6 readings,	Severe concomitant cardiovascular or non-cardiovascular diseases, and serum creatinine above 180 [mu]mol/L	Nitrendipine 10–20 mg once a day or 20 mg twice a day, if not controlled added captopril or hydrochlorothiazide 12.5 mg or 25 mg once or twice a day	Fatal CHD, non-fatal CHD, any CHD, fatal stroke, non-fatal stroke, any stroke	Median 3 years	89.3% in treatment arm and 90.8% in control arm
ADVANCE Collaborative Group 2007[c]	Patients of DM diagnosed at 30 years or older, with 55 years of age or older at entry to the study, a history of major CVD or at least one other risk factor for CVD	Definite indication for or contraindication to any of the study treatments , a definite indication for long-term insulin therapy at study entry	fixed dose combination of perindopril 2mg /day and indapamide 0.625mg /day with continuation of all other treatments except ACE inhibitors, those who tolerated and adhered, were assigned to fixed dose doubled after 3 months	Any CHD, any stroke	Median 4.3 years	73% in treatment arm and 74% in control arm
Schrier 2002[d]	Diabetic patients 40–74 years old, normotensive with DBP between 80-89 mmHg, not taking antihypertensive drugs,	Allergy to dihydropyridines or ACE inhibitors, MI or cerebrovascular event, or unstable angina during the past 6 months, coronary artery bypass surgery during the past 3 months, CHF, receiving dialysis, and/or serum creatinine above 3 mg/dL	Intensive: Nisoldipine or enalapril + conventional therapy if not controlled 1) Nisoldipine 10–20–40–60 mg/day or 2) enalapril 5–10–20–40 mg/day	Non-fatal MI, non-fatal stroke	Median 5.3 years	82.3% in treatment arm and 83.1% in control arm
SCAT 2000[e]	Age>=21 years, serum TC 4.1–6.2 mmol/L, LVEF>35%, no coronary angioplasty or bypass surgery within the past 6 months	Indication or contraindication to study drugs, other severe diseases, potential noncompliance	Enalapril 2.5 mg twice daily	Fatal CHD, non-fatal CHD, any CHD, non-fatal stroke	Median 5 years	84.3% in treatment arm and 86.9% in control arm
Wing 2003[f]	65-84 years of age, SBP >= 160 mmHg and DBP>= 90 mmHg at two sessions, absence of cardiovascular events within the past 6 months, willingness to participate	Any life-threatening illness, contraindication to ACE inhibitor or diuretic, plasma creatinine> 2.5 mg/dL, malignant hypertension, dementia	ACE inhibitor with or without Calcium channel blocker, beta blocker or Angiotensin receptor blocker	Fatal CHD, non-fatal CHD, any CHD, fatal stroke, non-fatal stroke, any stroke	Median 5 years	97.9% in treatment arm and 96.7% in control arm
Hansson 1999[g]	25–66 year-old patients with DBP>=100 mmHg on 2 separate occasions	Secondary hypertension, serum creatinine> 150 micromol/L, required treatment with beta blockers	Captopril (50 mg/day)	Any CHD, any stroke	Median 6.5 years	-
Beckett 2008[h]	Patients 80 years or older with persistent hypertension SBP between 160–199 mmHg	Contraindication to trial medication, accelerated HTN, secondary HTN, hemorrhagic stroke during the preceding 6 months, heart failure, serum creatinine above 1.7 mg/dL, gout, dementia, or requiring nursing care	indapamide + Perindopril (if BP uncontrolled) indapamide (1.5 mg sustained release), Perindopril 2 or 4 mg/day	Fatal CHD, fatal stroke, any stroke	Median 6.5 years	-

a) Bosch J, Yusuf S, Gerstein HC, Pogue J, Sheridan P, Dagenais G, et al. Effect of ramipril on the incidence of diabetes. *N Engl J Med*. 2006; **355:** 1551 – 1562.
b) Liu L, Wang JG, Gong L, Liu G, Staessen JA. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group. *J Hypertens*. 1998; **16:** 1823 – 1829.
c) Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007; **370:** 829 – 840.
d) Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int*. 2002; **61:** 1086 – 1097.
e) Teo KK, Burton JR, Buller CE, Plante S, Catellier D, Tymchak W, et al. Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation*. 2000; **102:** 1748 – 1754.
f) Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, et al. A comparison of outcomes with angiotensin-converting--enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003; **348:** 583 – 592.
g) Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet*. 1999; **353:** 611 – 616.
h) Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008; **358:** 1887 – 1898.

Web Table 4. Randomized clinical trials of thiazides and risk of coronary heart disease (CHD), or Stroke

Author and year (study acronym)	Study population	Exclusion criteria	Intervention groups	Outcome of interest	Follow-up	Compliance
HDFP 1979[a]	Hypertensive individuals from 30 to 69 year old who referred to 14 centers based on residential area and one center based on employment; the mean of 2nd and 4th DBP measurement be more than 90 mmHg	Bedfast and institutionalized persons	Stepped Care (SC): stepwise increase in medication in special centers: 1–**chlorthalidone (25-100mg/day)** 2– reserpine 3– hydralazine 4– guanethidine sulfate 5– other	Fatal CHD, fatal stroke	Maximum 5 years	77.8% in treatment arm and 58.3% in the control arm
HDFP 1982[b]	Hypertensive individuals from 30 to 69 year old who referred to 14 centers based on residential area and one center based on employment; the mean of 2nd and 4th DBP measurement be more than 90 mmHg	Bedfast and institutionalized persons	Stepped Care (SC): stepwise increase in medication in special centers: 1–**chlorthalidone (25-100mg/day)** 2– reserpine 3– hydralazine 4– guanethidine sulfate 5–other	Fatal stroke, non-fatal stroke, any stroke	Maximum 5 years	77.8% in treatment arm and 58.3% in the control arm
SHEP 1991[c]	Persons 60 years and above screened by mass mailing and community screening techniques persons 60 year and above not taking antihypertensives with mean of 2 measurements 160 to 219 mmhg for SBP and less than 100 mmhg for DBP, also those taking medication with SBP 130-219 and DBP less than 85 were referred for drug withdrawal before intervention	History and/or sign of major cardiovascular diseases and other major diseases	1–**chlorthalidone (12.5-25 mg/day)** 2– chlorthalidone doubled 3– atenolol 4–atenolol doubled	Fatal CHD, non-fatal CHD, any CHD, fatal stroke, non-fatal stroke, any stroke	Median 4.5 years	90% in treatment arm and 64% in the control arm
SHEP 1989[d]	Persons 60 years and above referring to 5 clinical centers in the US; with untreated essential systolic hypertension (SBP>=160 mmHg and DBP <=90 mmHg, 60 years old or older	History and/or sign of major cardiovascular diseases and other major diseases	**Chlorthalidone** 25 mg/day, doubled if BP is not controlled in 4 weeks	Fatal CHD, any CHD, fatal stroke, any stroke	Median 2.1 years	80% in treatment arm and 84% in the control arm
Amery 1985[e]	A multicenter study on elderly patients referring to the outpatient clinic 1) age above 60 years 2) SBP between 160–239 mmHg and DBP between 90–119 mmHg 3) patients› willingness to participate	1) curable causes of hypertension 2) complications of hypertension 3) concurrent diseases	hydrochlorothiazde 25 mg and **triamterene 50 mg**	Fatal CHD, any CHD, fatal stroke, any stroke	Median 4.68 years in placebo and Median 4.69 years in treatment group	96% in treatment arm and 98% in the control arm
Australian Therapeutic Trial 1980[f]	Australian or European volunteers who attendedscreeningcentersset up in Melbourne, Perth, and Sydney; age 30 to 69 years, DBP between 95 to 110 mmHG, SBP < 200 mmHg,	Hypertension treatment during the past 3 months, history of coronary disease, stroke, diabetes, asthma, gout, ECG abnormality, primary hypertension	Chlorothiazide 500 mg/day. If BP not controlled, methyl DOPA, propranolol, or pindolol were added. If BP not controlled, hydralazine or clonidine were added	Fatal CHD, non-fatal CHD, any CHD, fatal stroke, non-fatal stroke, any stroke	Median 4 years	61% in treatment arm and 56% in the control arm
Helgeland 1980[g]	All symptom-free Oslo men between 40 to 49 years of age and 7% between 20 to 39 years of age were invited and screened; age between 20-49 years, SBP>= 180 mmHG and DBP >=100 mmHG at 2 sessions	New or previous coronary heart disease, cardiovascular disease, intermittent claudication, CHF, valvular heart disease, drug-treated hypertension during the last year, diabetes, retinopathia, renal disease, hepatic disease, psychosis or neurosis, chronic or malignant diseases, secondary hypertension, ECG abnormalities	1) **Hydrochlorothiazide 50 mg/day 2) Alpha methyl DOPA 250–**500 mg **twice/day or propranolol** 40–**160 mg** twice/day	Fatal CHD, any CHD, any stroke	Median 5.5 years	99% in treatment arm and 97% in the control arm
MRC working party 1992[h]	The age-sex registers of 226 group practices throughout England, Scotland, and Wales attended by written invitation;men and women 65–74 years old with SBP 160-209 mmHg and DBP <115 mmHg	Subjects with known or suspected secondary hypertension, were taking antihypertensive drugs or medication for angina pectoris, had a history of MI, or stroke within the preceding three months; had impaired renal function; were diabetic; had asthma; had any serious intercurrent disease, including malignancy known to be present at the time of examination; or had a serum potassium concentration of 3–4 mmol/l or less or >5–0 mmol/l.	diuretic (amiloride and hydrochlorothiazide): 5 mg amiloride and 50 mg hydlochlorothiazide OR 2.5 mg amiloride and 25 mg hydlochlorothiazide	Fatal CHD, non-fatal CHD, any CHD, fatal stroke, non-fatal stroke, any stroke	Median 5.8 years	73% in treatment arm and 78% in the control arm
Staessen 1997[i]	Patients screened in 198 centers in 23 countries in western and eastern Europe;>=60 years old, with sitting SBP from 169 to 219 mmHg, standing SBP >=140 mmHg, DBP< 95mmHg,	Secondary systolic hypertension, retinal **hemorrhage or** papilloedema, congestive heart failure, **dissecting aortic aneurysm,** high serum creatinine, history **of nose bleeding,** stroke or MI **in the** preceding year, dementia, **substance abuse, ant severe concomitant** disease	**active tr**eatment by nitrendipine (20mg/day), if **neces**sary combined with or replaced by either **en**alapril (10mg/day) or hydrochlorothiazide (25mg/day) or both	Fatal CHD, non-fatal CHD, any CHD, fatal stroke, non-fatal stroke, any stroke	Median 2 years	92.5% in treatment arm and 91.7% in the control arm
Liu 1998[j]	Patient registration or population screening in 31 sys-China centers; Patients at least 60 years of age, consenting to participate, sitting SBP 160-219 mmHg averaged at 6 readings,	Severe concomitant cardiovascular or non-cardiovascular diseases, and serum creatinine above 180 [mu]mol/L	Nitrendipine (10–20 mg once a day or 20 mg twice a day), if not controlled added captopril and/or hydrochlorothiazide (12.5 mg or 25 mg once or twice a day each)	Fatal CHD, non-fatal CHD, any CHD, fatal stroke, non-fatal stroke, any stroke	Median 3 years	89.3% in treatment arm and 90.8% in the control arm
Dahlof 1991[k]	Patients referring to 116 health centers throughout Sweden; men and women 70–84 years of age with treated oruntreatedessentialhypertension, SBP >= 180 mmHg and DBP >=90 mmHg, DBP>=105 mmHg irrespective of SBP,	SBP **between >=230 mmHG** and/or **DBP>=120 m**mHg, isolated **systolic hypertension, orthostatic hypertension**, contraindication to **any drug, MI or stroke during the past year,** unstable angina requiring **treatment**, **other illnesses, unwillingness** to participate	Atenolol (50mg / day)+ hydrochlorothiazide (25mg/day) + amiloride (2.5mg/day)+ metoprolol (100 mg/day) or pindolol (5 mg/day)	Fatal MI, any MI, fatal stroke, any stroke	Median 2 years	84% in treatment arm and 77% in the control arm
Coope 1986[l]	Persons registered in 13 general practices in England and Wales invited to attend special screening clinics run by trial nurses; men and women 60–79 years old with SBP >= 170 or DBP >= 105 mmHg	Atrial fibrillation, AV heart block, ventricular failure, bronchial asthma, diabetes needing treatment or any life-threatening condition, untreated hypertension with SBP >280 or DBP >120 or treated patients within 3 months	Step 1: atenolol 100 mg, if BP not controlled: step 2: adding Bendrofluazide 5 mg. If BP not controlled: step 3: alpha methyl dopa 500 mg	Fatal CHD, non-fatal CHD, any CHD, fatal stroke, non-fatal stroke, any stroke	Median 4.4 years	
Veterans 1970[m]	Men (veterans) with mild to mod**erate** hypertension, aged 40–85 years old, **DBP 90-**114 mmHg not treated,	**Sev**ere **hyperten**sion and its complications, surgically curable **hypertension**, unrelated fatal diseases, unwillingness to participate	Hydrochlorothiazide (50 mg/day) +reserpine 0.1 mg twice daily) + hydralazine (25 mg three times daily)	Fatal CHD, non-fatal CHD, any CHD, fatal stroke, non-fatal stroke, any stroke	Median 3.8 years	84.5% in treatment arm and 86% in the control arm
Medical Research Council 1988[n]	Men and women screened in 14 centers; aged 35 to 64 years, sustained DBP between 90 to 109 mmHg,	History of definite MI during the past 3 months, angina, signs of cardiac failure, ECG abnormality	Bendrofluazide or propranolol (dose not mentioned)	Fatal CHD, non-fatal CHD, any CHD	Median 4.9 years	

a) Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. Hypertension Detection and Follow-up Program Cooperative Group. *JAMA*. 1979; **242:** 2562 – 2571.
b) Five-year findings of the hypertension detection and follow-up program. III. Reduction in stroke incidence among persons with high blood pressure. Hypertension Detection and Follow-up Program Cooperative Group. *JAMA*. 1982; **247:** 633 – 638.
c) Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA*. 1991; **265:** 3255 – 3264.
d) Perry HM, Jr., Smith WM, McDonald RH, Black D, Cutler JA, Furberg CD, et al. Morbidity and mortality in the Systolic Hypertension in the Elderly Program (SHEP) pilot study. *Stroke*. 1989; **20:** 4 – 13.
e) Amery A, Birkenhager W, Brixko P, Bulpitt C, Clement D, Deruyttere M, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet*. 1985; **1:** 1349-1354.
f) The Australian therapeutic trial in mild hypertension. Report by the Management Committee. *Lancet*. 1980; **1:** 1261 – 1267.
g) Helgeland A. Treatment of mild hypertension: a five year controlled drug trial. The Oslo study. *Am J Med*. 1980; **69:** 725 – 732.
h) Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. *BMJ*. 1992; **304:** 405 – 412.
i) Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet*. 1997; **350:** 757 – 764.
j) Liu L, Wang JG, Gong L, Liu G, Staessen JA. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group. *J Hypertens*. 1998; **16:** 1823 – 1829.
k) Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet*. 1991; **338:** 1281 – 1285.
l) Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. *Br Med J (Clin Res Ed)*. 1986; **293:** 1145 – 1151.
m) Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA*. 1970; **213:** 1143 – 1152.
n) Coronary heart disease in the Medical Research Council trial of treatment of mild hypertension. Medical Research Council Working Party on Mild Hypertension. *Br Heart J*. 1988; **59:** 364 – 378.