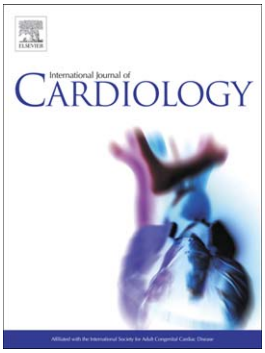

Potential health impact and cost-effectiveness of drug therapy for prehypertension

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Potential health impact and cost-effectiveness of drug therapy for prehypertension

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Authors' contributions

TC and DHY contributed to the conception and design of this study. TC, ZZZ, ZXJ, RQ and DHY carried out the acquisition, analysis and interpretation of data. TC, DHY and RQ wrote the first draft of the manuscript; VC, YMC and ZXJ revised the document for important intellectual content. All authors read and approved the final manuscript.

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Key words:

Cost-effectiveness analysis; hypertension; drugs; cardiovascular disease

Abstract

Background:

Studies have reported that pharmacologic interventions with candesartan or ramipril could reduce the risk of hypertension among prehypertensive subjects free of clinical cardiovascular disease(CVD), however, the cost-effectiveness and long-term cardiovascular risk of drug treatment among these population is unclear.

Method:

A Markov state-transition model was developed to simulate a hypothetical cohort of Chinese adults with high-range prehypertension (130-139/85-89 mmHg) but without CVD**.** Data on the incidence of CVD and hypertension was obtained from corresponding risk equations. Utility and disease-related costs were obtained from published literatures. Robustness and uncertainty was evaluated using deterministic and probabilistic sensitivity analyses.

Results:

Compared with placebo, drug treatment resulted in delaying the development of hypertension by nearly 12 years and reducing the absolute incidence of hypertension by 32.01% over lifetime. The cumulative incidence of coronary heart disease, stroke and heart failure were reduced and survival was improved from 28.46 to 28.80 years. The average incremental cost effectiveness ratio for drug treatment was $12,994 per quality-adjusted life-year and the value was mostly sensitive to the effect size of treatment and age starting treatment. At a willingness-to-pay threshold of >3×China gross domestic product per capita in 2014, there was a 30.48% chance that drug treatment would remain cost-effective and a low chance of being cost-effective if relative risk of treatment on hypertension was larger than 0.64.

Conclusion: Drug treatment for prehypertension may help stem the current epidemic of hypertension among Chinese adults free of CVD, which may in turn reduce CVD complications and potentially be cost effective.

Introduction

Hypertension is the leading risk factor for cardiovascular disease (CVD) in China and it contributes to 2.33 million cardiovascular deaths in 2005[1]. Despite tremendous efforts to promote healthful lifestyles and drug treatment rate, the prevalence of hypertension has increased from 20% among men and 17% among women in 2002 to 31.2% and 28.0%, respectively, in 2009[2, 3]. The term of "prehypertension" was introduced in Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII) to highlight an at-risk population. It is believed that prehypertension is a precursor of clinical hypertension and successfully control this population would reduce the potential cardiovascular burden [4].

Currently, the treatment of prehypertension is primarily nonpharmacological lifestyle changes such as healthy dietary habits, overweight/obesity control [5]. However, an important obstacle to the success of these strategies is that lifestyle modification treatments are difficult to maintain and may require large-scale social and policy changes as well as the patients himself [5]. The trial of preventing hypertension(TROPHY) study was the first trial to perform pharmacological intervention amongst individuals with prehypertension. Results from TROPHY suggested that treatment with Candesartan significantly reduced the incidence of hypertension, even after discontinuing drug therapy for 2 years [6]. This is in agreement with another clinical trial (prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure(PHARAO) study) performed in Germany [7]. In this study, Ramipril is proved to be effective in reducing the incidence of office hypertension by 34.4%.

However, there are no studies to assess whether early drug treatment of prehypertension can reduce its long-term cardiovascular consequences.

Additionally, nearly 30% of the general adult population in China have prehypertension and the health and economic consequences caused by prehypertension are substantial [8-10]. It is important that an effective strategy must be carefully chosen on the basis of both public health and economic reasons. However, we are still unclear whether prescribing drugs among individuals with prehypertension but without clinical CVD is cost-effective, given the relatively low absolute risk amongst this population [11, 12].

The aim of our study was to combine data from published clinical trials and epidemiological studies to predict 1) medium and long-term hypertension incidence and its associated cardiovascular risk and 2) the lifetime cost-effectiveness of pharmacological therapy versus placebo intervention among individuals with prehypertension free of CVD.

1. Method

2.1 Model structure

We adopted a similar approach to develop a state-transition Markov model used by Herman et al for the primary prevention of type 2 diabetes mellitus in adults with impaired glucose tolerance [13]. Our model simulated the progression from prehypertension to onset of hypertension, to hypertension with complications and death. Simultaneously, this model allowed individuals with prehypertension to move to CVD/death directly (**Figure 1**). In total, we modelled the following 10 distinct health states: (1) healthy with prehypertension; (2) hypertension; (3) stroke; (4) post stroke; (5) coronary heart disease(CHD); (6) post CHD; (7) heart failure (HF); (8) post HF; (9) CVD mortality and (10) non-CVD mortality. After each cycle, cohort

members were redistributed to one of the above ten health states. Individuals reaching a CVD state by the end of the first year could subsequently transit to another state (e.g., the occurrence of stroke after HF). Subsequent to a primary event, patients might move to a chronic heath state (post CHD or post HF or post stroke), which had a higher risk to suffer a new CVD event or death. Due to the lack of data, some states were not modelled (e.g., myocardial infarction after post-stroke). Subjects transiting to hypertension had a similar pathway as those with prehypertension, but they could not return to prehypertension (linear model without remission) and had a different pre-specified transition probability. The detailed transition pathways could be found in the **online supplementary Figure A1** to **Figure A5.**

In this study, we simulated two cohorts: one that followed individuals who received placebo treatment (placebo intervention) and the other one which followed individuals who were prescribed antihypertensive treatment (drug treatment). This will keep consistence with the two completed trials[6-7] after considering the fact that no head-to-head clinical trials were performed to compare drug treatment, intensive lifestyle changes and usual care. All prehypertensive individuals entered the model with their pre-specified characteristics and were followed along the disease paths until they turned 100 years old or died. The model cycle length was 1 year, and half-corrections were applied. A more detailed description for the base-case study population could be found in the **online supplementary file**.

2.2 Transition probability

The values for the transition probabilities and other inputs were mainly obtained from published evidences among Chinese population and summarized in **Table 1**. A prediction model for hypertension risk was used for estimating hypertension incidence rate [14]. The incidence of each primary CVD events (stroke, HF and CHD) was

derived from their corresponding risk equations reported in studies [15-17] on the basis of individual data from Nanjing Community Cardiovascular Risk Survey study [18]. This will keep the correlation between each of the risk factors. The distribution for each risk factors among participants with prehypertension and hypertension could be found in **online supplementary Table A3** and **Table A4**. As the age in this study was mainly from 30 to 75 years old, exponential interpolation was employed to smooth the age-specific annual rates to persons older than 75 years (**online supplementary Figure A6** and **A7**). A detailed description for the estimation of primary CVD event rate could be found in the **online supplementary file**.

Each primary event might be followed by secondary events or chronic conditions, and individual who experienced a first non-fatal cardiovascular event would have a higher risk of sequelaes. As there were no suitable risk equations to calculate the risk for each age/sex stratum among Chinese population, transition probabilities for subsequent events (within or more than 1 year after a primary event) were drawn from registries and/or meta-analysis studies [19-24]. These rates were varied in sensitivity analyses (**online supplementary Table A5**). However, for the sake of conservative estimation, the probabilities of new events in any of the post-CVD states were not adjusted their different blood pressure (BP) categories.

As evidences in the published literature demonstrated that prehypertension may be associated with higher CVD mortality, we separated mortality into CVD and non-CVD mortality [1, 8]. Age- and sex-specific risks of all-cause/CVD mortality were derived from Chinese National Statistical Office in 2013[25]. The non-CVD mortality risks were recalculated after exclusion of CVD death from the total mortality and this was assumed to be unaffected by the states in the model.

2.3 Treatment effect

Antihypertensive treatment could significantly decrease the risk of CVD morbidity or mortality by lowering BP among patients with hypertension as well as those with clinical history of CVD but without hypertension [26-28]. However, trials to date could only indicate a deceasing risk of incident hypertension, rather than a reduction in CVD risk among prehypertensive individuals without prior CVD [6, 7, 11]. Our model only incorporated the benefits of drug treatment in hypertension incidence, and made the conservative assumption of no effect in CVD risk (**Table 1**).

2.4 Cost

Costs data were obtained from multiple sources, including the China Health Statistics Yearbook report and health economics researches (**Table 1)**. For costs of prehypertension, we assumed it was the same as those with hypertension, although the dose for this specific population may be lower. This approach could be justifiable because it would lead to a conservative estimate. In our model, we used the data from a cost-effectiveness and an observational study [29, 30]. For costs of CVD events during year 1, the values were obtained from several recently published articles which included detailed breakdown costs (eg, drug cost, salary costs of primary healthcare providers) [31-34]. Cost of recurrent stroke or MI were captured by applying the same cost of first-year events. The costs were estimated from a health system perspective and were inflated to the 2014 price level using the average rate of inflation in China from 2009 to 2014 and converted to US dollars (6.25 Yuan≈1 USD 2014). A more detailed description for cost estimation could be found in the **online supplementary file**.

2.5 Utility

The utility measured in a 2008 survey in China was applied to individuals without CVD [35]. We derived utility weight of CHD, stroke or HF from a published cost-

effectiveness study [36], as the preference weights for them were not available in Chinese population (**Table 1**). Quality-adjusted life-years (QALYs) were calculated by multiplying the length of time spent in a certain health state by the utility associated with that health state.

2.6 Base-case analysis

We used results from the Nanjing Community Cardiovascular Risk Survey study as a proxy for participants with prehypertension [18]. On average, members of the cohort had a mean age of 50.5 years, were 54.4% female, had a mean systolic blood pressure(SBP), diastolic blood pressure(DBP) and body mass index(BMI) of 131.9mmHg, 82.4 mmHg, 24.5 kg/m^2 , respectively. Using our base-case cohort, we assessed the simulated 5-year, 10-year and lifetime cumulative incidence of hypertension, CVD events and life expectancy by the method of Markov model cohort simulation. Incremental cost-effectiveness ratios (ICERs) were also calculated by dividing the incremental change in total healthcare costs by the incremental change in QALYs. The degree of cost-effectiveness was evaluated based on the WHO Choosing Interventions That Are Cost Effective (highly cost-effective, ICER less than the gross domestic product(GDP) per capita; moderately cost-effective, ICER of 1-3×GDP per capita; and not cost-effective, ICER of>3×GDP per capita) [37]. The gross domestic product(GDP) per capita of China in 2014 was reported to be $7,593.9 from the World Bank report [38]. Cost and utility would be both discounted at a 3% annual rate in the future for the primary projections. All analyses were conducted using a life-time horizon unless otherwise indicated.

2.7 Analysis of uncertainty

The impact of uncertainty in model variables on the ICER was tested by a series of sensitivity analyses. First, in the 1-way sensitivity analysis, each input parameter was

varied over a set of plausible ranges provided in **Table 1** and **online supplementary Table A5**. Second, a two-way sensitivity analysis was performed to assess how large the changes of the first two key inputs must be in order to exceed the cost-effective threshold (ICER of >3×GDP per capita=$22,782). Third, in order to assess how sensitive the results were to variations in simultaneous changes of several variables, we also conducted a probabilistic sensitivity analysis (PSA). We ran our model for 5,000 repetitions using a Monte Carlo simulation and at each simulation a value for each of the 54 model parameters were randomly selected based on their respective distributions, which were shown in **Tables 1** and **online supplementary Table A5**. In our model, probabilities, prevalence rates, and preference weights were assumed to follow a beta distribution, and cost data were assumed to follow a gamma distribution. Additionally, uniform and triangular distributions were used where appropriate. The incremental cost-effectiveness scatter plot and acceptability curve were constructed to test the uncertainty of ICER from the derived 5,000 pairs of incremental cost and QALYs between these two strategies.

2. Results

3.1 Model validation

The findings from our model indicated a reasonable concordance between model predictions and national life tables (30.20 vs. 31.31 for women, 26.69 vs. 27.21 for men). Our results showed that the 5-year absolute cardiovascular risk (except HF) was relatively low (2.58%), however, each event rate was found to be within reported ranges (**online supplementary Tables A6**).

3.2 Base-case analysis

Using baseline estimates, our model simulated the lifetime cumulative incidence of hypertension, which was shown in **online supplementary Tables A8**. The figure indicated that approximately 30% of individuals with placebo would develop hypertension within 5 years, however, it would take more than 17 years to achieve that percent for those prescribed antihypertensive medication. Thus, compared to placebo, the drug intervention delayed the onset of hypertension by about 12 years. Over a lifetime, prescribing drugs among individuals with prehypertension would reduce the risk for developing hypertension by 32.01% (**Table 2**).

Table 2 summarizes the potential changes in CVD events and life expectancy as well as costs, which may be caused by the delaying or reduction of hypertension risk. In general, risk reductions in CHD, stroke and HF were observed for all different time horizons. The reduction in mortality or clinical event risk from drug treatment increased life expectancy by 0.34 years and QALYs by 0.22 (undiscounted: 0.09), whereas it increased discounted costs from $3,690.1 to $4,859.5 (an increment of $1,169.4). Therefore, based on the WHO criteria, the discounted lifetime ICERs might be moderately cost-effective ($12,994 per QALY within ICER of 1-3×GDP per capita).

3.3 Uncertainty analysis

Our cost-effectiveness analysis was relatively insensitive to a variety of alternative assumptions (**online supplementary Figure A9**), specifically for those relating to secondary CVD events. The 10 individual parameters that were most influential in ICER estimates. were RR of hypertension on treatment, age starting treatment, BMI, drug treatment costs, discount rate, SBP, utility of stroke, incidence of stroke among hypertensive persons, utility of non-CVD state, and DBP.

A two-way sensitivity analysis was performed to investigate the relationship of the two most influential variables (RR of hypertension on treatment and age starting treatment). At a willingness-to-pay threshold of $22,870 per additional QALY (3 times the GDP), our model indicated that the probability of being cost-effective increased with age and decreased with the higher RR of hypertension on treatment, but there was low probability if the RR of treatment was larger than 0.64 (**online supplementary Figure A10**).

To further reflect the uncertainty in the estimates, the incremental cost-effectiveness scatter plot was derived from PSA (**online supplementary Figure A11**). In comparison with placebo, prescribing drug to participants with prehypertension would result in an increase in QALYs in 99.70% of simulations. Regarding the incremental costs, drug treatment for prehypertension would decrease costs in 5.87% of simulations. Overall, the cost-effectiveness for drug treatment was 30.48% with a maximum willingness to pay to be $22,870 per additional QALYs. Also, we found an increasing probability of being cost-effective if the decision maker was willing to pay more for an additional health gain, and a 5.80% of the probability that drug

intervention was cost-saving (**Figure 2**).

3. Discussion:

This study provides evidence that drug treatment with the angiotensin-converting enzyme inhibitor ramipril or the angiotensin receptor antagonist candesartan for prehypertension, as compared with placebo intervention, could delay and/or prevent hypertension by approximately 12 years over a lifetime, which would result in a reduction in cardiovascular complications and an increase in life expectancy. In addition, when patients' preferences and cost of treatment were both taken into account, we found that prescribing drugs among prehypertension was moderately cost-effective, costing $12,994 per QALY.

In comparison with other currently accepted medical interventions for hypertension or CVD, our study found a relative smaller life-year or CVD gains from our base-case model [36, 39-42]. For example, our models projected that an antihypertensive intervention would prolong life expectancy of prehypertensive individuals by 0.34 years. By contrast, Tsevat et al [39] predicted that BP control could increase gains in life expectancy of 2.3 and 1.7 years in men and women, respectively. Geisler et al [36] estimated that renal denervation substantially increased median survival from 17.1 years to 18.4 years and reduced cardiovascular mortality by 30% and all-cause mortality by 15%. We also found a comparable benefit showing metformin interventions could only improve survival by 0.2 years among drug therapy in adults with impaired glucose tolerance [13]. We believed that the relative smaller benefits in our study may be ascribed to the relatively low absolute risk of CVD for this specific population (prehypertension but without CVD) and assumption of no effect on CVD incidence by drug treatment.

In general, the overall conclusions of the cost-effectiveness analysis for our study were robust to the ranges of uncertainty surrounding utility weights, and costs as well

as treatment effect. Although it seemed that the judgment of cost-effectiveness was most sensitivity to the RR of antihypertensive treatment, it was still important that health policy should be based on what is determined to be an acceptable ICER. The acceptable ICER from our relative low CVD risk population (2.58% of 5-year CVD risk) may support the concept of using predicted baseline CVD risk equations to guide blood pressure-lowering treatment decisions, not just the BP levels [26, 43, 44]. This is because prehypertensive subjects often exhibited several additional risk factors (e.g., dyslipidemia, obesity) and could have the same absolute CVD risk with those with hypertension [10, 12]. The idea of implementing intensive BP control in high-risk patients was confirmed by SPRINT trial, which may partly support our study results.

Several limitations need to be acknowledged in our study. First, due to the lack of evidences to show the benefits on CVD risk by drug treatment among prehypertensive subjects without CVD, our model only captured the benefit of hypertension risk and assumed no direct benefits on stroke, CHD, and HF. This limitation might underestimate the benefit and result in conservative estimates. Second, we did not incorporate the rate of drug side effects and their associated costs in our model, however, it is anticipated to have little influence on the final evaluation as both studies reported a comparable and low rate of serious adverse events between groups and no concerns were raised for adverse reactions caused by drug [6, 7]. Third, as there are no reports discussing the medication compliance of a life-long drug treatment among these healthy prehypertensive adults, a potential impact on our result may deserve more attentions. Fourth, many key inputs into the model were derived from Chinese population and we did not know whether our results were transferable to other countries, especially considering the large variations in costs from different countries. Finally, as all computer simulation studies, we were clear that average gains

in life expectancy or ICER from the prediction models may not apply to the individual patient, and therefore results need to be interpreted with caution.

In summary, our model projected that drug treatment in prehypertensive Chinese adults free of CVD could delay and/or prevent onset of hypertension and its complications. This policy may be cost-effective and reasonable, but are highly dependent on the treatment effectiveness.

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Figure titles and legends:

Figure 1: Schematic Depiction of the Model

Hypertension module; prehypertension module; MI module; HF module; Stroke module

Figure 2: Cost-effectiveness acceptability curve

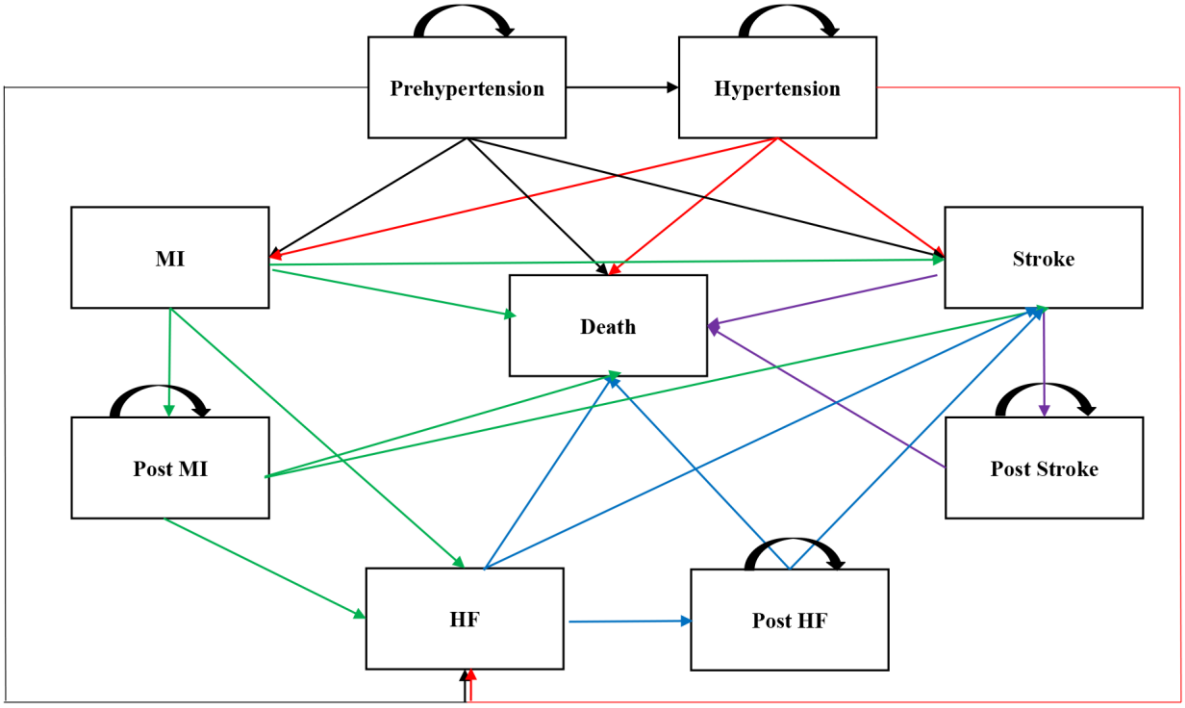

Figure 1

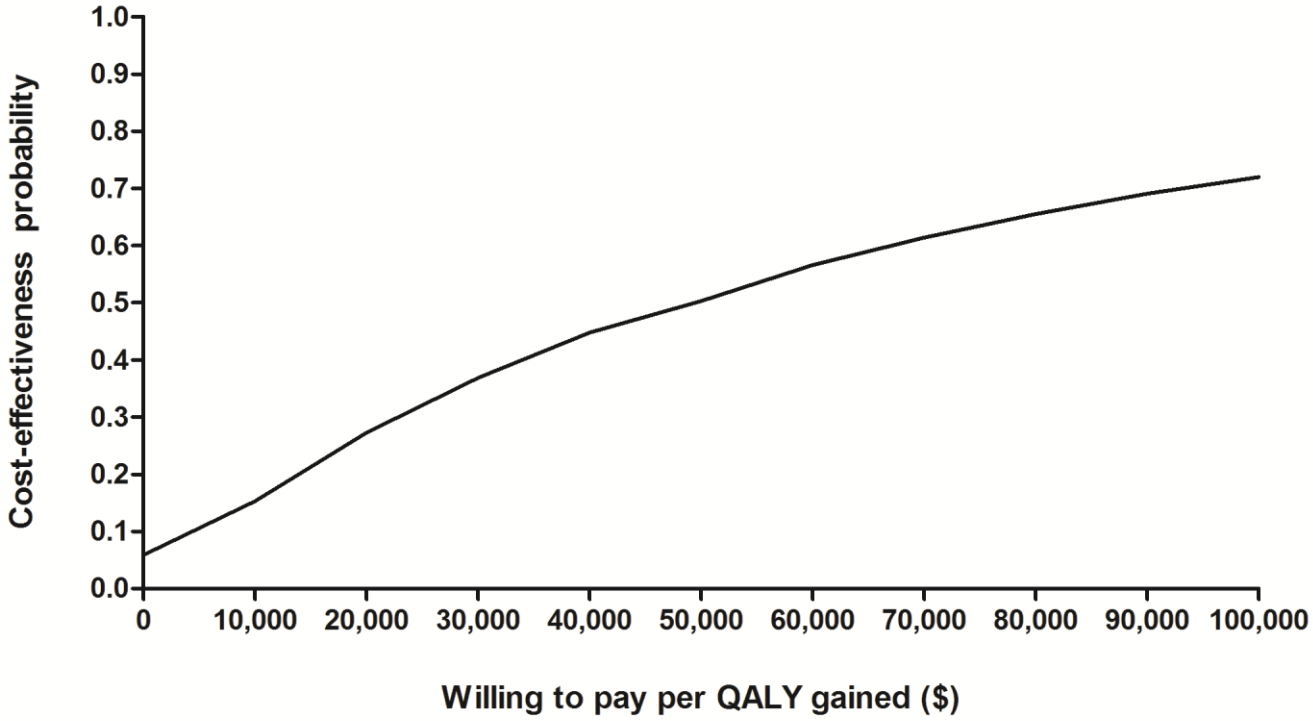

Figure 2

Table 1 key model parameters

Data input	Base Case Numeric Value (Range) or Survival Model (Covariates)	Distribution	Reference
Age	50.5 (30-80)years	Triangular	[18]
Sex	54.4(0-100)% female	Beta	[18]
BMI	24.5(20-30)kg/m^2	Normal	[18]
SBP	131.9(120-139)mmHg	Triangular	[18]
DBP	82.4(65-89)mmHg	Triangular	[18]
Hypertension incidence	Weibull(age, sex, BMI, SBP, DBP)	±25% uniform	[14]
CHD incidence	Exponential (age, sex, DBP, SBP,TC, HDL, DM, Smoking)	±25% uniform	[16]
Stroke incidence	Exponential (age, sex, DBP, SBP, FHS, AF, DM)	±25% uniform	[17]
HF incidence	Exponential (age, sex, SBP, DM, LVH, BMI, heart rate, CHD, valve disease)	±25% uniform	[15]
All-cause mortality	Age and sex dependent	±25% uniform	[25]
Stroke mortality	First year: 12.3% for male, 17.8% for female; beyond: SMR 2.23(1.29–3.88) on background mortality	Beta/ Lognormal	[19-21]
CHD mortality	First year: 5.7%; beyond: SMR 1.43(1.18–1.72) on background mortality	Beta/ Lognormal	[20, 22]
HF mortality	First year: 15.9%; beyond: 8%	Beta	[23, 24]
Effect of treatment			
RR of hypertension on treatment	0.34(0.25-0.95)	Triangular	[6, 7]
Cost			
Annual cost for Antihypertensive treatment	$161.44($53.76-$484.32)	Gamma	[29, 30]
Annual cost for Stroke	$3358.11($1,118.88-$10,074.24) first year, post $1,315.16($438.24-$3,945.44)	Gamma	[25, 31, 32]
Annual cost for CHD	$4,820.89($1,606.88-$14,462.56) first year, post $382.08($160.64-$1,446.24)	Gamma	[25, 33]
Annual cost for HF	$1,260.16($420-$3,780.48) first year, post $293.92($97.92-$881.76)	Gamma	[25, 34]
Quality of life weights(utilities)			
No cardiovascular disease	Age and sex dependent	±25% uniform	[35]
Stroke	0.63 (0.26 to 0.92)	Beta	[36]
CHD	First year: 0.76 (0.5 to 0.87); beyond: 0.88 (0.67 to 0.94)	Beta	[36]
HF	0.71 (0.43 to 0.84)	Beta	[36]

Discount rate	3% (0%-5%)	Uniform	Assumed

AF: atrial fibrillation; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; DM: diabetes mellitus; TC: total cholesterol; HDL: high-density lipoprotein; FHS: family history stroke; HF: heart failure; LVH: left ventricular hypertrophy; CHD; coronary heart disease; RR: relative risk

Table 2 Base-Case Results

	5-year time horizon				10-year time horizon				lifetime horizon			
Outcomes	Placebo Intervention	Drug Treatment	RD	RR	Placebo Intervention	Drug treatment	RD	RR	Placebo Intervention	Drug treatment	RD	RR
Hypertension	31.37	11.80	19.57	0.38	51.17	20.85	30.32	0.41	80.66	48.65	32.01	0.60
CHD,%	0.80	0.79	-0.01	0.99	1.83	1.73	-0.10	0.95	12.53	12.30	-0.23	0.98
Stroke,%	1.46	1.42	-0.04	0.97	3.49	3.21	-0.28	0.92	26.89	25.41	-1.48	0.94
HF,%	0.95	0.90	-0.05	0.95	2.22	2.00	-0.22	0.90	12.82	12.65	-0.17	0.99
CV mortality,%	0.59	0.57	-0.02	0.97	1.64	1.53	-0.11	0.93	22.96	22.56	-0.40	0.98
All-cause mortality,%	3.08	3.06	-0.02	0.99	7.31	7.19	-0.12	0.98				
Life years									28.46	28.80	0.34	
Undiscounted QALYs									20.43	20.65	0.22	
QALYs discounted,3%									13.46	13.55	0.09	
Cost discounted($),3%									3690.1	4859.5	1169.4	
Discounted ICER										$12,994/QALY		

CHD; coronary heart disease; HF: Heart failure; QALYs: quality adjusted life years; ICER: incremental cost-effectiveness ratio; RD: risk difference; RR: relative risk