Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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SUPPLEMENTARY MATERIALS

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SUPPLEMENTARY METHODS

Structure of the Model

The Cardiovascular Disease (CVD) Policy Model is a computer-simulation, state-transition (Markov cohort) model of coronary heart disease and stroke incidence, prevalence, mortality, and costs in the U.S. population over age 35 years.[1-3] The Demographic-Epidemiologic Submodel predicts coronary heart disease and stroke incidence and non-CVD mortality among subjects without CVD, stratified by age, sex, and up to 8 additional categorized risk factors estimated from weighted United States National Health and Nutrition Examination Survey (NHANES) data from 2007-2010 (**Appendix Figure 1**). Risk factors include: systolic blood pressure (<140, 140-159.9, ≥160), isolated diastolic blood pressure (normal systolic blood pressure and diastolic blood pressure (90-99 or ≥100 mmHg), antihypertensive medication treatment status (self-reported), smoking status (active smoker, non-smoker with exposure

to environmental tobacco smoke, non-smoker without environmental exposure), high density lipoprotein (HDL) cholesterol (<1.0, 1.0-1.5, ≥1.6 mmol/L; <40, 40-59.9, ≥60 mg/dL), low-density lipoprotein (LDL) cholesterol (<2.6, 2.6-3.3, ≥3.4 mmol/L; <100, 100-129.9, ≥130 mg/dL), body mass index (<25, 25-29.9, ≥30 kg/M^2), diabetes mellitus (yes or no), and chronic kidney disease [estimated glomerular filtration rate of < 60 ml/min (using the Modifcation of Diet in Renal Disease formula), and/or proteinuria (spot albumin/creatinine ration > 200 μg/g)]. After CVD develops, the Bridge Submodel characterizes the initial stroke or coronary heart disease event (cardiac arrest, myocardial infarction, or angina) and its sequelae for 30 days. Then, the Disease History Submodel predicts subsequent CVD events, coronary revascularization procedures, CVD mortality, and non-CVD mortality among patients with CVD, stratified by age, sex, and history of events. The general chronic CVD categories are coronary heart disease only, stroke only, and combined prior coronary heart disease and prior stroke. Each state and event has an annual cost and quality-of-life adjustment as well as an annual probability of a repeat event and/or transition to a different CVD state. All population distributions, risk factor levels, coefficients, event rates, case fatality rates, costs, and quality-of-life adjustments can be modified for forecasting simulations.

Data Sources

Version 4 of the CVD Policy Model includes data from prior versions as well as many updates and upgrades.[1-3] The 2010 U.S. Census provides the baseline population[4] and number of 35 year-olds projected to enter the model population from 2010-2060.[5, 6] CHD and stroke deaths in 2010 were extracted from U.S. Vital Statistics.[7] Deaths were categorized according to the International Classification of Diseases (ICD) 10 codes[8]: I20-I25 and two-thirds of I49, I50, and I51 were used to estimate coronary heart disease deaths,[9] I60-I69 were used to estimate stroke deaths, and all other deaths were considered non-CVD deaths.

The incidence of coronary heart disease and stroke were based on competing risk Cox proportional hazards analysis of the Framingham Heart Study[10] and the Framingham Offspring Study[11] cohorts from 1988-2007, with further adjustment for risk factor differences between the Framingham cohorts and the contemporary U.S. population represented by the NHANES. Incident coronary heart disease events were allocated to angina pectoris, hospitalized myocardial infarction, or cardiac arrest. Prevalence, joint distributions and means of U.S. risk factor values were estimated from pooled, survey design-weighted NHANES, 2007-10.[12] Annual transition rates between risk factor levels were calculated to preserve age-range trends over time. Risk function betas for non-blood pressure risk factors were estimated separately for the risk of incident coronary heart disease events, incident strokes , and non-CVD deaths, using examinations 1-8 of the Framingham Offspring cohort.[11] The Framingham coefficients have been useful across many populations.[13-16] Risk factors were assumed to affect the incidence of myocardial infarction, arrest, and angina in proportion to the overall incidence of coronary heart disease, except tobacco smokers were assumed to have a higher relative risk for infarction and arrest ([17]; personal communication, Sean Coady, National Heart, Lung, and Blood Institute, February, 2006) and a proportionately lower coefficient for angina. Environmental tobacco exposure was assumed to carry a relative risk of 1.26 for myocardial infarction and cardiac arrest compared with non-exposed non-smokers[18] but not to influence angina.

Baseline CVD Policy Model inputs for the year 2010 were within 1% of all targets obtained from U.S. national data sources (**Appendix Table 1**).

Preliminary analyses suggested that the strength of the observational association between blood pressure and CVD risks in the Framingham Heart Study fell short of the strength of association observed in antihypertensive treatment trials (basis of comparison was the Law, Morris, and Wald trials meta-

analysis summary estimates) .[19] Starting with CVD Policy Model default blood pressure beta coefficients estimated from Framingham Heart Study data, we calibrated the coefficients in order to 1) reproduce the association of change in systolic BP estimated from both the Prospective Cohort Studies Collaborative, and 2) a large pooled analysis of BP treatment trials by Law, Morris, and Wald.[19] A U.S. NHANES-based cohort representing the age and sex structure and mean systolic BP of the U.S. stage one and stage two hypertensive population was prepared for calibration simulations. In order to simulate the average trial pooled in the Law, Morris and Wald study, five year treatment duration was simulated. First, a base case was simulated or 2010-2014 with no change in 2010 blood pressure levels. A 2010-2014 intervention simulation followed in which systolic BP was lowered by approximately 10 mm Hg or diastolic blood pressure was lowered 5 mm Hg in each age and sex category. Beta coefficients were calibrated until the Prospective Cohort Studies Collaboration age- and sex- specific relative risks were matched within 0.02 or less (**Appendix Table 2**). Summary (age and sex weighted) relative risk with a 10 mm Hg systolic or 5 mm Hg diastolic blood pressure change for ages 35-74 years of 0.75 was within the 95% confidence limits of the treatment trials relative risks estimated in the Law, Morris, and Wald meta-analysis for coronary heart disease (target interval 0.73-0.83), as was the estimate for stroke (estimate 0.64; target interval 0.52-0.67; **Appendix Table 3**).

In order to ensure that the systolic BP relative risk inputs were not over-fitted to the calibration targets, and not representative of the results of a real clinical trial, we set out to use the model to simulate the landmark Systolic Hypertension in the Elderly Program (SHEP), a double-blind placebo-controlled trial of antihypertensive adults aged 60 and older. By analyzing individual participant-level data, we were able to enter the characteristics of the SHEP intervention arm and control arms (age, baseline systolic BP, mean HDL and LDL cholesterol, and smoking status of participants). We then simulated the SHEP trial over a five-year period (mean follow up in SHEP lasted 4.5 years). Cox proportional hazards analysis of

SHEP was performed in order to ensure that we could reproduce the estimates reported in the 1999 SHEP trial report, and we performed original analyses of SHEP data in order estimate the total stroke (fatal and nonfatal), and total and fatal coronary heart disease relative risks associated with BP treatment consistent with CVD Policy Model definitions.

For each of stroke and CHD, we simulated RRs of stroke and CHD, assuming baseline characteristics of the SHEP cohort and systolic blood pressure beta coefficients used in our main analysis (these based on the Prospective Cohort Studies Collaboration and Law, Morris, Wald meta-analysis of trials as described above). Stroke and CHD RRs resulting from the simulated trial were then compared with the main estimates and 95% confidence intervals of the observed effects reported by the SHEP trial (Appendix Table 4).

Compared with the results observed in the actual trial, our five-year simulation of the SHEP trial resulted in nearly perfectly matched results for reductions in the rate of coronary heart disease events with treatment. For stroke, our simulations yielded a 30% reduction in strokes (relative risk 0.70) compared with the 36% reduction observed in the trial (relative risk 0.64). SHEP excluded potential participants if they had a history of atrial fibrillation, but our Model cannot selectively do so. Since five-year effects of antihypertensive treatment are unlikely to lower risk for stroke caused by atrial fibrillation, the inclusion of people with atrial fibrillation likely explains why our simulated reduction of nonfatal stroke was less than that observed in SHEP. If we adjust our total stroke relative risk for an assumed 15% of all strokes (fatal and nonfatal) due to atrial fibrillation,[20] and unaffected by the BP lowering intervention, our simulated trial would yield a relative risk of total stroke of 0.66 (calculated as: $\exp[1.15*\ln(0.70)]$), very close to the SHEP total stroke relative risk of 0.64.

The number of hospitalized myocardial infarctions was obtained from discharges coded as ICD-9 code 410 in the 2010 National Hospital Discharge Survey (NHDS)[21] adjusted for likely miscoding,[22] such as patients who were discharged alive after two days or fewer without a percutaneous coronary intervention, and transfer patients. Case-fatality rates and rates of myocardial infarction in subgroups were estimated from national data[21] and a variety of complementary sources.[23-25] Prehospital arrest deaths were estimated from the U.S. Vital Statistics,[26] and out-of-hospital cardiac arrests surviving to hospital discharge were estimated from national data[21]. Survival after a coronary heart disease event was estimated using California data on the ratio of in-hospital survival to 30 day survival[27] and data from Medicare and Seattle, Washington.[28, 29] Rates of coronary revascularizations were estimated from the National Hospital Discharge Survey,[21] with mortalities estimated from aggregrated historical data.

Stroke incidence was assumed to independent of the risk of new onset coronary heart disease in the same year. The number of hospitalized strokes was also obtained from the 2010 NHDS. Positive predictive values of specific ICD-9 stroke hospital diagnosis codes (inclusive of ICD 9 codes 430-438) were derived by pooling several studies of stroke incidence that compared hospital diagnoses with a gold standard (e.g., stroke ascertained by Atherosclerosis in Communities Study, the Rochester Epidemiology Study or similar criteria).[30] The positive predictive values were applied to age- and sex-specific NHDS cases in order to estimate total stroke event rates (inclusive of first-ever and recurrent stroke events). Applying 30-day case fatality rates based on the Atherosclerosis in Communities Study[31, 32] yielded annual mortality rate estimates within the range of stroke rates reported by the U.S. Centers for Disease Control (CDC Wonder) for 2010. Incidence calibration assumed that 77% of all strokes are incident (first ever),[33] but it was assumed that the proportion first ever/total diminished with age (i.e., >90% of all strokes are first strokes in 35-44 year olds and 50% are first strokes in 85-94 year olds). The resulting incidence of hospitalized stroke approximated age and sex specific stroke incidence rates

observed in U.S. stroke cohort and surveillance studies. The annual probabilities of stroke after myocardial infarction[34] and the probability of coronary heart disease in stroke patients was based on natural history studies.[35-40]

The background prevalence of CVD by age, sex, and CVD disease state (stroke, coronary heart disease, or both stroke and coronary heart disease) in 2010 was estimated from the National Health Interview Survey data from 2009-2011,[41] assuming that the imperfect positive predictive value of survey data is offset by its imperfect sensitivity.[42-44] Age-specific prevalences for individual CVD disease states were fitted with polynomial or spline functions of age to obtain smooth, monotonically increasing prevalences. The background prevalence of prior coronary revascularization was estimated from revascularizations before 2010 and estimated survival after revascularization, while model projections were used to infer the distribution of revascularization by CVD state.

Age and sex specific health care costs were estimated using national data.[45] Hospitalized stroke and coronary heart disease costs and acute stroke rehabilitation costs were estimated using 2008 California hospital data,[46] deflated using cost to charge ratios[47] and the ratio of the U.S. national average costs to the California average.[48] Chronic outpatient CVD costs additional to average background health care costs for the first year after the event and for subsequent years were estimated for patients with a stroke or coronary heart disease diagnosis surveyed in the U.S. Medical Expenditure Panel Surveys (MEPS) pooled from 1998-2008. Average annual non-cardiovascular (background) costs were also estimated from the MEPS.[49] All model costs were indexed to the year 2010 using the medical component of the consumer price index. Health-related quality-of-life weights and severity distributions for disease states were based on the Global Burden of Disease disability weights study.[50-52]

Blood pressure treatment assumptions

Each recommendation made by the 2014 U.S. hypertension guidelines committee was backed by review of multiple studies and assessment of the variable quality of the evidence was made explicit. However, for a quick overview of the committee's treatment recommendations, the reader may access the 2014 Hypertension Guideline Management Algorithm (http://files.jamanetwork.com/jn/Algo_image.png). In brief, after a trial period of lifestyle interventions geared at reducing blood pressure, patients with hypertension selected for pharmacologic treatment were grouped into those with or without diabetes or chronic kidney disease (CKD). The blood pressure targets for those treatment groups are shown in manuscript **Table 1**. Those without those conditions were categorized into Nonblack and Black. For initial choice of antihypertensive agent, Nonblack patients were recommended to start with any of thiazide diuretic, angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) or calcium channel blocker (CCB). Black patients were recommended the same initial choice of therapies, except were not recommended to start with an ACE. Patients without diabetes but without CKD wer recommended the same options as above for non-diabetics (options based on if the patient is Nonblack or Black). Patients with chronic kidney disease were recommended to start with an ACE or an ARB. Should the patient require more than one medication to reach target blood pressure, the guideline recommended any of the following: 1) maximize the first medication to full dose, then add a second agent; 2) add the second agent before maximizing the dosage of the first, or 3) start with two medication classes in combination. The 2014 committee did not recommend any particular frequency of blood pressure monitoring in treated patients, so our analysis used recommendations from the prior nation al guideline as well as the observed number of visits needed to achieve hypertension control in the ALLHAT trial (manuscript **Table 2**).

In keeping with the 2014 hypertension guidelines, we did not choose to simulate the effects of any particular medication; instead we simulate "standard dose" effects and assumed average drug prices across classes. Examples of standard doses for different antihypertensive medications can be found at http://www.wolfson.qmul.ac.uk/bpchol/a3.pdf, and include nifedipine 30 mg daily, amlodipine 5 mg daily, lisinopril 10 mg daily, hydrochlorothiazide 25 mg daily, and losartan 50 mg daily, Especially in patients with higher BPs (e.g. stage two hypertension), medications are added sequentially and BP lowered gradually over time. The amount of blood pressure change was assumed to be a function of the pre-treatment or baseline BP and the effect of a standard-dose antihypertensive agent at that pre-treatment level (**Appendix Table 5**). It is important to note that for patients with very high BPs (mean systolic BP of 185 mm Hg or more) it was assumed that even with taking four standard dose medications, these patients would on average achieve a BP of about 143 mm Hg, near, but not at, the target of 140 mmHg.

Appendix Table S1. Comparisons of selected CVD Policy Model simulation outputs for 2010 (model base year) with national targets for 2010.

Age and sex category	Total myocardial infarctions Target sources: NHDS		Total strokes Target source: NHDS		CHD deaths Target source: national vital statistics		Stroke deaths Target source: national vital statistics		All-cause deaths Target source: national vital statistics	
	Target	**Model**	**Target**	**Model**	**Target**	**Model**	**Target**	**Model**	**Target**	**Model**
Males										
35-44	13,979	13,839	16,535	16,553	4,783	4,862	1,027	1,031	43,345	43,335
45-54	56,129	55,811	43,493	43,710	19,489	19,594	3,298	3,301	111,981	111,933
55-64	77,992	77,395	67,863	68,497	38,032	38,065	6,159	6,133	190,845	190,629
65-74	75,804	75,689	79,450	79,239	45,700	46,096	9,350	9,265	231,327	231,231
75-84	62,982	63,063	76,205	76,436	64,610	65,097	16,215	16,240	312,778	312,873
85-94	37,568	37,483	38,943	39,247	64,071	63,958	15,318	14,742	264,705	263,235
Females										
35-44	6,259	6,144	6,390	6,387	1,710	1,822	873	875	26,538	26,619
45-54	17,071	17,035	36,952	37,083	6,858	6,969	2,609	2,764	71,145	71,352
55-64	40,246	40,403	42,966	43,222	15,122	15,265	4,622	4,605	122,502	122,546
65-74	43,843	43,898	69,473	69,659	24,964	25,137	8,504	8,308	178,530	178,342
75-84	60,097	60,043	93,040	93,434	53,247	53,600	21,492	21,541	313,803	313,894
85-94	57,661	57,403	77,481	77,883	99,680	98,988	35,416	36,233	448,864	447,244
Deviation from target		**-0.26%**		**0.39%**		**0.27%**		**0.12%**		**-0.14%**

Appendix Table S2. Results of the systolic blood pressure calibration exercise. FHS = Framingham Heart Study. PCS= Prospective Cohort Studies Collaboration. CVDPM = CVD Policy Model inputs and simulation outputs.

		Beta coefficients (per 1.0 mm Hg systolic BP)						Relative risks (after 10 mm Hg SBP lowering or 5 mm Hg diastolic BP lowering)					
		CHD			Stroke			CHD			Stroke		
Age/sex category	Mean change in SBP (mm Hg)	FHS default	PCS target	CVDPM (input)	FHS default	PCS target	CVDPM (input)	FHS default	PCS target	CVDPM (output)	FHS default	PCS target	CVDPM (output)
Males													
35-44	9.57	.0217	.0361	.0325	.0215	.0513	.0500	.78	.71	.73	.73	.61	.60
45-54	10.38	.0176	.0353	.0310	.0196	.0496	.0460	.81	.70`	.72	.75	.61	.59
55-64	10.38	.0135	.0330	.0300	.0178	.0453	.0420	.78	.71	.73	.76	.63	.62
65-74	10.88	.0094	.0285	.0265	.0159	.0385	.0370	.75	.74	.76	.76	.66	.66
Females													
35-44	9.87	.0217	.0360	.0320	.0215	.0513	.0470	.71	.70	.72	.79	.60	.60
45-54	10.35	.0176	.0353	.0320	.0196	.0496	.0450	.72	.70	.72	.77	.61	.60
55-64	10.94	.0135	.0330	.0295	.0178	.0452	.0414	.73	.70	.72	.73	.62	.61
65-74	11.68	.0094	.0285	.0245	.0159	.0385	.0345	.73	.73	.75	.77	.65	.65

Appendix Table S3. Comparison of CVD Policy Model trial simulation to Law Morris Wald meta-analysis of anti-hypertensive medication treatment trials, both assuming a systolic blood pressure change of 10 mm Hg or a diastolic blood pressure change of 5 mm Hg.

Outcome	Law, Morris, and Wald meta-analysis estimate	CVD Policy Model main estimate Males	CVD Policy Model main estimate Females
Coronary heart disease	0.78 (0.73—0.83)	Ages 35-74 years: 0.75 Ages 35-64 years: 0.74	Ages 35-74 years: 0.74 Ages 35-64 years: 0.73
Stroke	0.59 (0.52—0.67)	Ages 35-74 years: 0.64 Ages 35-64 years: 0.62	Ages 35-74 years: 0.63 Ages 35-64 years: 0.62

Appendix Table S4. Results of a simulated trial of blood pressure treatment in participants in the Systolic Hypertension in the Elderly Program (SHEP) trial, using relative risk inputs and transition probabilities in the CVD Policy Model version used for the analysis.

SHEP Population RR (SBP lowering of 12 mmHg for 5 years)		
Outcome	Actual SHEP paper RR and 95% CI	CVD Policy Model five year simulation results with PSC calibrated SBP betas [overall rate ratio (95% uncertainty interval)*]
Incident stroke	0.64 (0.50-0.82)	0.70 (0.66-0.75)
Incident coronary heart disease†	0.75 (0.60-0.94)	0.76 (0.73-0.79)

*95% uncertainty intervals derived from 1,000 probabilistic simulations that sampled from within the 95% confidence intervals of age- and sex-specific Prospective Cohorts Studies Collaboration beta coefficients.

†SHEP incident coronary heart disease defined as first-in-trial nonfatal acute myocardial infarction, coronary revascularization, or coronary heart disease death. CVD Policy Model incident coronary heart disease defined as first-ever nonfatal acute myocardial infarction, angina pectoris with or without coronary revascularization, or coronary heart disease death.

Appendix Table S5. Sequential changes in blood pressure with successive standard dose medications, based on the trials-based blood pressure change prediction formulas of Law, Morris, and Wald.[19]

	Mean start BP	BP change 1 drug	new BP	BP change 2nd drug	new BP	BP change 3rd drug	new BP	BP change 4th drug	new BP	Final BP change	
Systolic blood pressure (mm Hg changes)										**< 60 years old**	**≥ 60 years old**
effect of 4 std dose	185	12.2	172.8	11.0	161.8	9.9	151.9	8.9	143.0	42.0	33.1
effect of 3.5 std doses	175	11.2	163.8	10.1	153.7	9.1	144.6	6.3	138.4	36.6	21.3
	179	11.6	167.4	10.4	157.0	9.4	147.6	6.5	141.1		
effect of 3 std doses	165	10.2	154.8	9.2	145.6	8.3	137.4			27.6	19.4
	169	10.6	158.4	9.5	148.9	8.6	140.3				
effect of 2 std doses	155	9.2	145.8	8.3	137.5					17.5	
effect of 1 std dose	155	9.2	145.8							9.2	
effect of 1 std dose	147	8.4	138.6							8.4	
effect of 0.5 std dose	142	6.1	135.9							6.1	
effect of 0.5 std dose	155	7.1	147.9								7.1
Diastolic blood pressure (mm Hg changes)										**All ages**	
effect of 3 std doses	107	6.6	100.5	5.9	94.6	5.2	89.4			17.7	
effect of 3 std doses	104	6.3	97.7	5.6	92.1	5.0	87.2			16.8	
effect of 3 std doses	105	6.3	98.2	5.6	92.5	5.0	87.5			17.0	
effect of 3 std doses	105	6.4	98.6	5.7	92.9	5.1	87.9			17.1	
effect of 3 std doses	103	6.2	97.2	5.5	91.7	4.9	86.8			16.6	
effect of 3 std doses	107	6.6	100.5	5.9	94.6	5.2	89.4			17.7	
effect one std dose	94	5.2	89.0							5.2	
effect one std dose	94	5.2	88.8							5.2	
effect one std dose	93	5.1	88.0							5.1	
effect of 0.5 std dose	94	4.1	90.1							4.1	
effect of 0.5 std dose	94	4.1	89.9							4.1	

Appendix Table S6. Costs, medication-related adverse event incidence, quality of life, adherence, and discount rate assumptions used for the comparative effectiveness analysis of U.S. BP treatment guidelines

Annual costs per person treated (2010 costs; inflated to 2014 costs in all results)				
MD office visit				
Treatment monitoring visits (number)	4	3	5	ALLHAT trial (Heidenreich et al.[53]), JNC7 recommendation.
Stage 2 hypertension	3	2	4	
Stage 1 hypertension	$71	Not modeled	Not modeled	Outpatient visit, Medicare Physician Fee Schedule (code 99213, non-facility limiting charge)[54]
Cost per routine monitoring visit				
Hospitalization				
Average cost (used for infrequent hospitalized drug-related adverse events)	$12,000	Not modeled	Not modeled	National Inpatient Sample survey
High cost (used for rare hospitalized drug-related adverse events)	$21,000			
Laboratory test (electrolytes monitoring on treatment)				
Number of tests	1	1	2	JNC7 recommendation
Cost per test	$15	Not modeled	Not modeled	Centers for Medicare and Medicaid laboratory fee schedule[55]
Antihypertensive drug costs (total daily doses)***				
0.5 standard doses	$124	Not modeled	$296	Average wholesale prices reported by manufacturers ("Red Book"; 2010),[56] see Methods text for estimation method
1.0 standard dose	$166		$363	
1.5 standard doses	$215		$409	
2.0 standard doses	$238		$567	
3.0 standard doses	$357		$850	
3.5 standard doses	$430		$1,311	
4.0 standard doses	$496		$1,374	
Pharmacy dispensing fees	$27		$33	

Acute and chronic CVD treatment costs				
Myocardial infarction hospitalization				
Nonfatal	$33,000			California Office of Statewide Health Planning and Development (OSHPD) hospital data, 2008[57]
Fatal	$46,000			
Coronary revascularization procedures				
Percutaneous coronary intervention	$21,000-$23,000			
Coronary artery bypass graft surgery	$57,000-$59,000			
Stroke				
Fatal	$21,000-$26,000			
Nonfatal	$15,000-$21,000			
Chronic coronary heart disease costs				
First year	$11,000			
Subsequent years	$2,000			U.S. Medical Expenditure Panel Surveys (MEPS), 1998-2008[58]
Chronic post-stroke costs				
First year	$16,000			
Subsequent years	$5,000			
Inflation from 2010 to 2014 costs	9%		11%	Main = change in general U.S. consumer price index; upper = change in medical component
Serious adverse effects of medications (incidence per 100,000 person-years)				
Common, outpatient management				Based on Law 2003[59]
three standard doses	10,039.20	6,950.21	12,742.06	
two standard doses	7,572.41	5,242.43	9,611.13	
one standard dose	5,200.00	3,600.06	6,600.00	
one-half standard dose	2,600.00	1,800.00	3,300.00	
Infrequent, hospitalized				trials, medication labels, post-marketing reports
three standard doses	193.06	19.31	965.31	
two standard doses	145.62	14.56	728.12	
one standard dose	100.00	10.00	500.00	
one-half standard dose	50.00	5.00	250.00	
Rare, hospitalized/severe				
three standard doses	1.93	0.0193	19.31	
two standard doses	1.46	0.0146	14.56	

one standard dose	1.00	0.0100	10.00	
one-half standard dose	0.50	0.0050	5.00	
Death				
three standard doses	0.0193	0.0002	0.1931	
two standard doses	0.0146	0.0001	0.1456	
one standard dose	0.0100	0.0001	0.1000	
one-half standard dose	0.0050	0.0001	0.0500	
Utility (QALY weight penalty, duration)				
Drug side effects managed as outpatient (1 d)	0.23			Montgomery[60]
Drug side effect requiring hospitalization (1d)	0.50			Clinical judgment
Acute stroke (1 m)	0.86			GBD 2010 Study[61]
Chronic stroke survivors (12 m)	0.85--0.88			
Acute myocardial Infarction (1 m)	0.91			
Acute unstable angina (1 m)	0.95			
Chronic CHD (12 m)	0.91—0.98			
Death	1.00			
Disutility due to taking daily medications	0.00		0.01-- 0.02	Past cost-effectiveness analyses[54, 55, 62]
Adherence to medications (percent of patients continuing prescribed treatment)	75%	25% or 50% lower than observed in trials	Not modeled	Law, Morris and Wald meta-analysis for main estimate[19]
Annual discount rate	3%	Not modeled	Not modeled	Assumed

Appendix Table S7. Annual population treated and cost-effectiveness of implementing JNC 8 hypertension treatment guidelines in all previously untreated adults with hypertension aged 35-74 years, the CVD Policy Model. Average annual results from a years 2014-2024 simulation.

Males

	Ages 35-59 years						Ages 60-74 years					
Strategy	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER
Status quo		195,000	49,100	32,548,707	44,162			292,000	96,500	46,204,464	20,924	
Base case: treat CVD patients to 140/90, compared with status quo	251,000	193,000	48,300	32,389,198	44,164	Cost-saving	454,000	284,000	93,500	45,608,476	20,932	Cost-saving
Stage one, primary prevention (compared with base case)	2,394,000	179,000	46,200	31,922,497	44,187	Cost-saving	1,353,000	271,000	90,700	45,005,183	20,954	Cost-saving

Females

	Ages 35-59 years						Ages 60-74 years					
Strategy	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER
Status quo		101,000	20,600	20,256,506	44,995			204,000	56,400	30,970,745	23,201	
Base case: treat CVD patients to 140/90, compared with status quo	133,000	100,000	20,400	20,233,485	44,996	Cost-saving	29,000	199,000	54,600	30,708,052	23,206	Cost-saving
Stage one, primary prevention (compared with base case)	1,584,000	97,000	20,000	20,334,623	45,002	17,700	503,000	188,000	52,600	30,498,158	23,221	Cost-saving

Appendix Table S8. Average annual population treated and cost-effectiveness of implementing U.S. hypertension treatment guidelines in all previously untreated adults aged 35-74 years with stage 2 hypertension (DBP >= 100 mm Hg if age 35-59 years; BP >= 160/100 mm Hg if age >=60 years), the CVD Policy Model.

Males

	Ages 35-59 years						Ages 60-74 years					
Strategy	Number newly treated	CVD events	CVD deaths	Total costs (thousands)	Total QALYs (thousands)	ICER	Number newly treated	CVD events	CVD deaths	Total costs (thousands)	Total QALYs (thousands)	ICER
Status quo		195,000	49,100	32,548,707	44,162			292,000	96,500	46,204,464	20,924	
Base case: treat CVD patients to 140/90	251,000	193,000	48,300	32,389,198	44,164	Cost-saving	454,000	284,000	93,500	45,608,476	20,932	Cost-saving
Stage 2, primary prevention, compared with base case	838,000	184,000	47,100	31,910,683	44,177	Cost-saving	1,110,000	277,000	91,900	45,202,418	20,944	Cost-saving

Females

	Ages 35-59 years						Ages 60-74 years					
Strategy	Number newly treated	CVD events	CVD deaths	Total costs (thousands)	Total QALYs (thousands)	ICER	Number newly treated	CVD events	CVD deaths	Total costs (thousands)	Total QALYs (thousands)	ICER
Status quo		101,000	20,600	20,256,506	44,995			204,000	56,400	30,970,745	23,201	
Base case: treat CVD patients to 140/90	133,000	100,000	20,400	20,233,485	44,996	Cost-saving	316,000	199,000	54,600	30,708,052	23,206	Cost-saving
Stage 2, primary prevention, compared with base case	283,000	99,000	20,300	20,203,812	44,998	Cost-saving	849,000	191,000	53,200	30,471,357	23,216	Cost-saving

Appendix Table S9. Average annual population treated and cost-effectiveness of implementing U.S. hypertension treatment guidelines in all previously untreated males and females aged 35-59 years with stage 1 hypertension (BP >= 90-99 mm Hg or 140-159 mm Hg) and with diabetes or chronic kidney disease, the CVD Policy Model.

	Males																	
	Ages 35-44 years						Ages 45-59 years						Ages 60-74 years					
Strategy	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER
Status quo		30,000	6,000	5,814,034	18,133			165,000	43,200	26,734,672	26,030			292,000	96,500	46,204,464	20,924	
Base case	60,000	30,000	5,800	5,802,734	18,133	Cost-saving	191,000	163,000	42,400	26,586,464	26,031	Cost-saving	454,000	284,000	93,500	45,608,476	20,932	Cost-saving
Stage one, primary prevention (compared with base case)	191,000	29,000	5,800	5,808,145	18,133	13,100	478,000	156,000	42,200	26,558,006	26,033	Cost-saving	980,000	281,000	92,800	45,482,721	20,937	Cost-saving

	Females																	
	Ages 35-44 years						Ages 45-59 years						Ages 60-74 years					
Strategy	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER
Status quo		11,000	2,500	3,495,301	17,964			89,000	18,200	16,761,206	27,031			204,000	56,400	30,970,745	23,201	
Base case	27,000	11,000	2,400	3,497,209	17,964	79,800	112,000	89,000	18,000	16,736,276	27,032	Cost-saving	351,000	199,000	54,600	30,708,052	23,206	Cost-saving
Stage one, primary prevention (compared with base case)	110,000	12,000	2,400	3,509,906	17,964	124,800	746,000	88,000	17,900	16,753,691	27,033	16,300	635,000	197,000	54,200	30,717,887	23,208	3,500

Appendix Table S10. Average annual population treated and cost-effectiveness of implementing U.S. hypertension treatment guidelines in all previously untreated males and females aged 35-59 years with stage 1 hypertension (DBP 90-99 mm Hg or SBP 140-159 mm Hg) and without diabetes or chronic kidney disease, the CVD Policy Model.

Males

	Ages 35-44 years						Ages 45-59 years					
Strategy	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER
Status quo		30,000	6,000	5,814,034	18,133			165,000	43,200	26,734,672	26,030	
Base case	60,000	30,000	5,800	5,802,734	18,133	Cost-saving	253,000	163,000	42,400	26,586,464	26,031	Cost-saving
Stage one, primary prevention (compared with base case)	793,000	30,000	5,700	5,872,551	18,135	40,700	1,100,000	160,000	42,000	26,553,673	26,037	Cost-saving

Females

	Ages 35-44 years						Ages 45-59 years					
Strategy	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER
Status quo		11,000	2,500	3,495,301	17,964			89,000	18,200	16,761,206	27,031	
Base case	21,000	11,000	2,400	3,497,209	17,964	79,800	112,000	89,000	18,000	16,736,276	27,032	Cost-saving
Stage one, primary prevention (compared with base case)	262,000	11,000	2,400	3,547,326	17,964	181,600	713,000	88,000	17,800	16,786,921	27,034	22,200

Appendix Table S11. Average annual population treated and cost-effectiveness of implementing U.S. hypertension treatment guidelines in all previously untreated males and females aged 60-74 years with stage 1 hypertension (BP >= 90-99 mm Hg or 140-159 mm Hg) and without diabetes or chronic kidney disease, the CVD Policy Model.

	Males					
	Ages 60-74 years					
Strategy	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER
Status quo		292,000	96,500	46,204,464	20,924	
Base case	454,000	284,000	93,500	45,608,476	20,932	Cost-saving
Stage one, primary prevention (compared with base case)	1,078,000	282,000	93,100	45,565,786	20,936	Cost-saving
	Females					
	Ages 60-74 years					
Strategy	Number newly treated	CVD events	CVD deaths	CVD costs (thousands)	Total QALYs (thousands)	ICER
Status quo		204,000	56,400	30,970,745	23,201	
Base case	351,000	199,000	54,600	30,708,052	23,206	Cost-saving
Stage one, primary prevention (compared with base case)	678,000	198,000	54,400	30,743,749	23,207	21,000

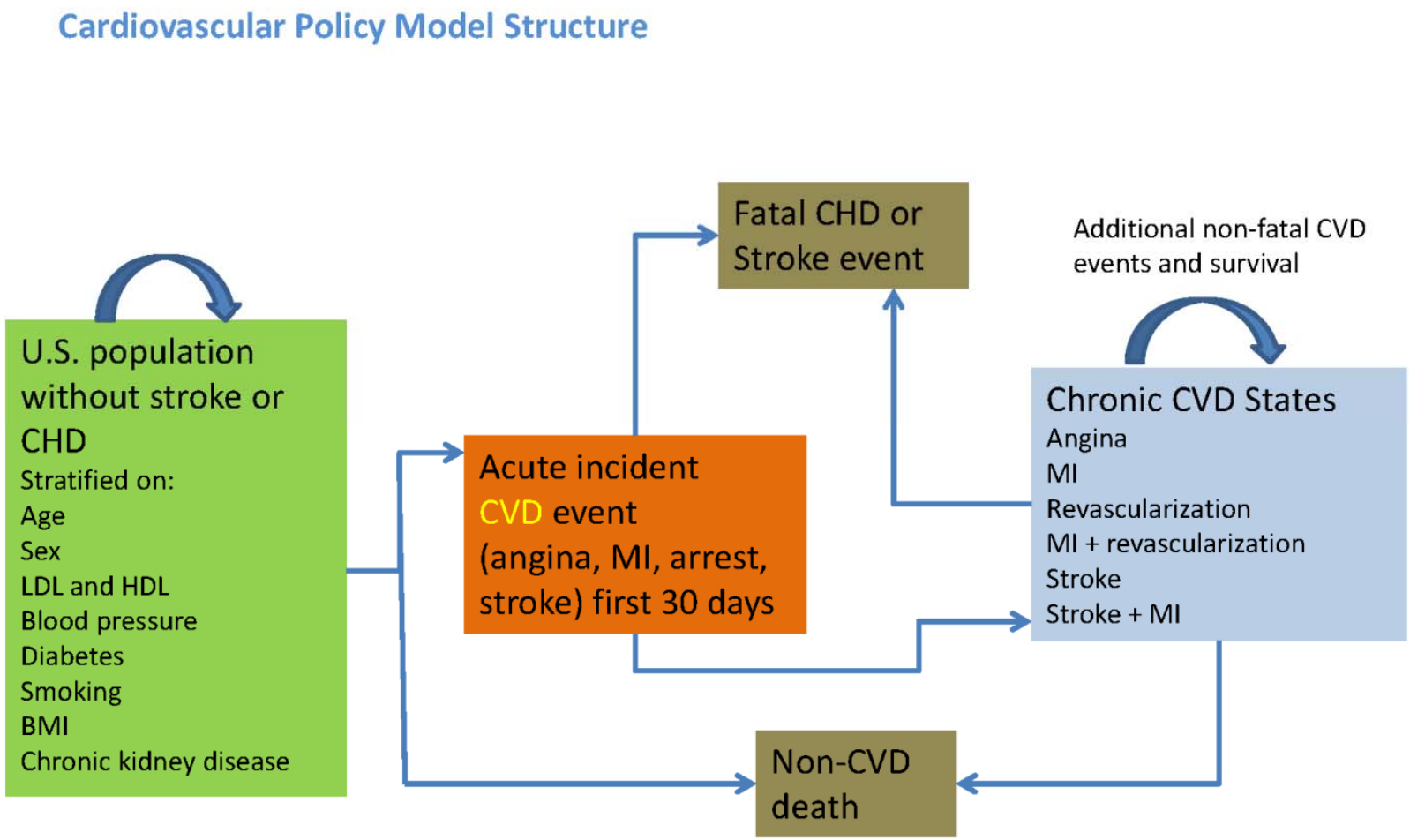
Appendix Table S12. One-way senstivity analyses. Data are ICERs compared with the base case. CS = cost-saving.

Sensitivity analysis	Males						Females					
	age 35-59			ages 60-74			age 35-59			ages 60-74		
	all stage 2	stage 1, DM/CKD	stage 1, no DM or CKD	all stage 2	stage 1, DM/CKD	stage 1, no DM or CKD	all stage 2	stage 1, DM/CKD	stage 1, no DM or CKD	all stage 2	stage 1, DM/CKD	stage 1, no DM or CKD
Results using main input assumptions	cs	cs	5,000	cs	cs	cs	cs	25,800	39,400	cs	3,500	21,000
Effectiveness												
Blood pressure change with treatment												
Higher	cs	cs	cs	cs	cs	cs	cs	11,700	21,500	cs	cs	7,800
Lower	cs	6,300	27,500	cs	cs	3,500	cs	51,300	74,000	cs	13,700	47,600
Relative risk for CHD or stroke with change in BP												
Lower bound	cs	cs	cs	cs	cs	cs	cs	14,900	21,700	cs	cs	12,800
Upper bound	cs	1,100	21,900	cs	cs	cs	5,000	38,100	60,600	cs	14,100	31,600
Relative risk for non-CVD death												
Lower bound	cs	cs	2,400	cs	cs	cs	cs	15,400	21,900	cs	2,800	9,100
Upper bound	cs	cs	4,600	cs	cs	cs	cs	50,500	74,100	cs	25,300	**harmful***
Adherence (incremental to adherence in treatment trials												
50%	cs	cs	cs	cs	cs	cs	cs	19,100	30,500	cs	cs	18,800
75%	cs	cs	1,800	cs	cs	cs	cs	22,700	35,200	cs	1,200	20,500
Costs												
Medication costs												
Higher	cs	35,200	44,600	cs	2,000	15,500	33,800	97,600	99,700	4,000	53,200	82,100
Frequency of monitoring												
Higher	cs	9,800	30,100	cs	cs	100	cs	56,900	77,300	cs	25,000	40,700
Lower	cs	cs	cs	cs	cs	cs	cs	11,900	22,800	cs	cs	15,700
Add estimated non-cardiovascular disease cost savings	cs	cs	cs	cs	cs	cs	cs	cs	cs	cs	cs	cs
Quality of life												
Higher side effect frequency	cs	cs	15,700	cs	cs	cs	cs	39,100	55,400	cs	12,500	30,300
Lower side effect frequency	cs	cs	400	cs	cs	cs	cs	20,000	32,300	cs	cs	16,600
Pill-taking disutlity												
Lower pill-taking disutility	cs	lost QALYs†	lost QALYs†	cs	cs	lost QALYs†	cs	lost QALYs†	lost QALYs†	cs	lost QALYs†	lost QALYs†
Higher side effect frequency	cs	lost QALYs†	lost QALYs†	129,300	lost QALYs†	lost QALYs†	lost QALYs†	lost QALYs†	lost QALYs†	lost QALYs†	lost QALYs†	lost QALYs†
Lag in medication effectiveness												
One year lag in medication benefits; full costs	cs	cs	5,200	cs	cs	cs	cs	26,500	40,600	cs	3,600	21,500
Cost inflation calculation												
Calculate inflation using medical component of consumer price index	cs	cs	5,100	cs	cs	cs	cs	26,300	40,300	cs	3,600	21,500

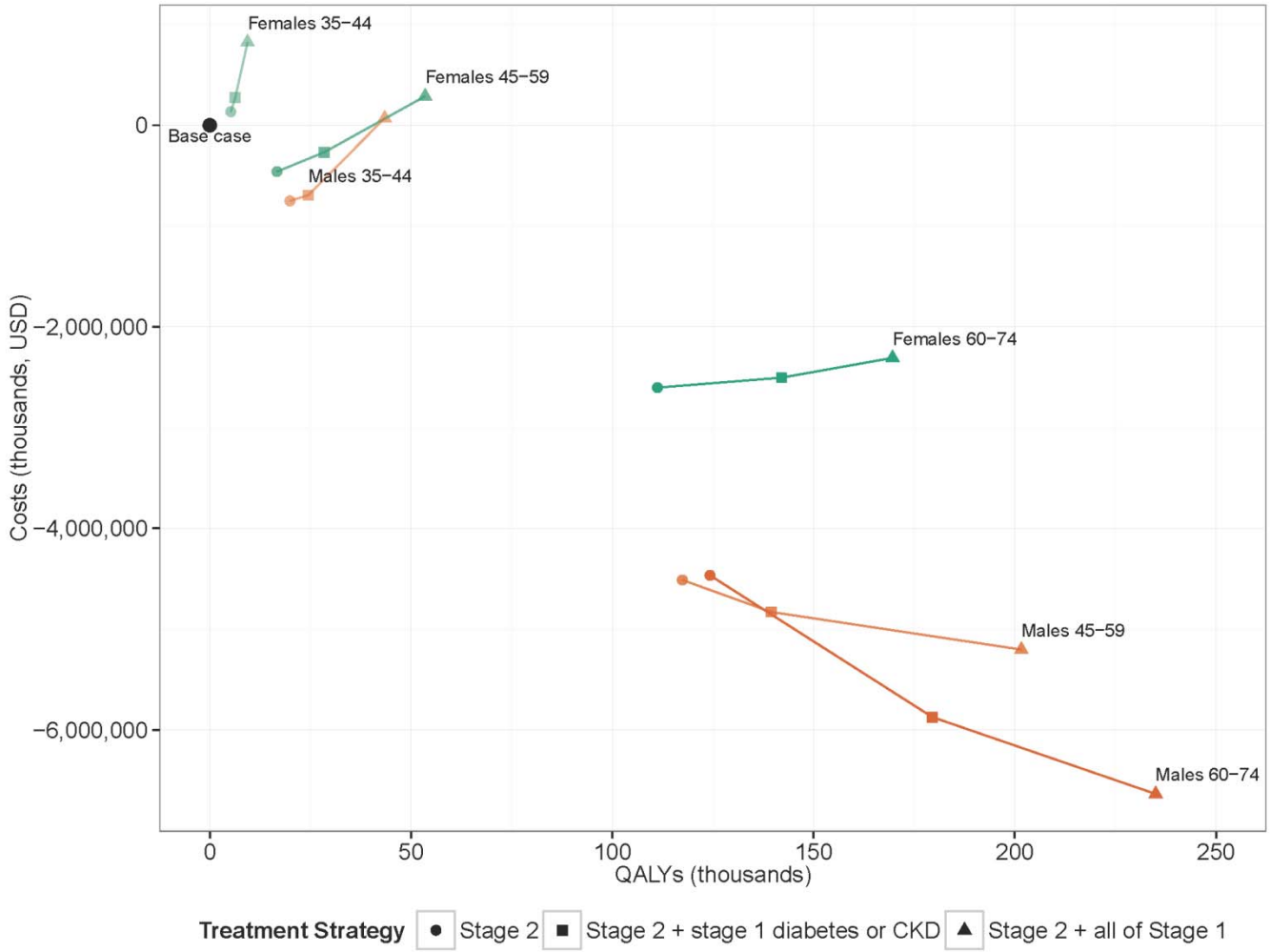
*Under this assumption, the intervention would lead to a loss of QALYs compared with the base case

†Willingness to forego healthy life years gained in order avoid taking pills resulted in net loss of QALYs. Lower disutility assumption meant that on average patients would forego 30 days of healthy life gained over 10 years in order to avoid taking antihypertensive medications. High disutility meant patients would forego 60 days of healthy life gained over 10 years in order to avoid taking antihypertensive medications.

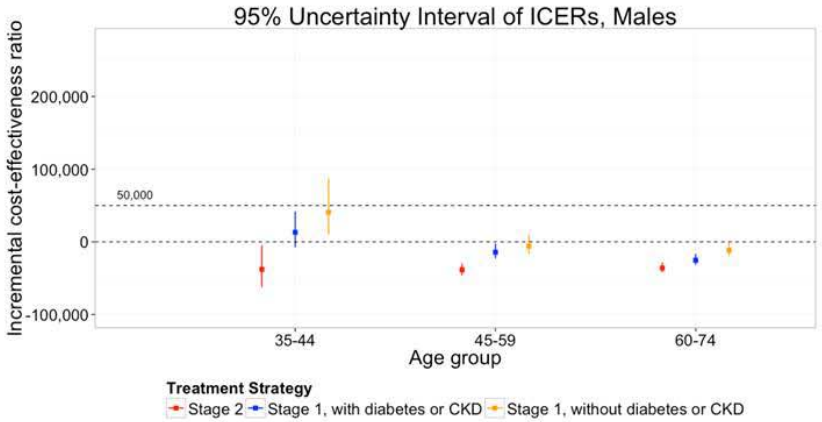
Appendix Figure S1. Cardiovascular Disease Policy Model structure and disease states.

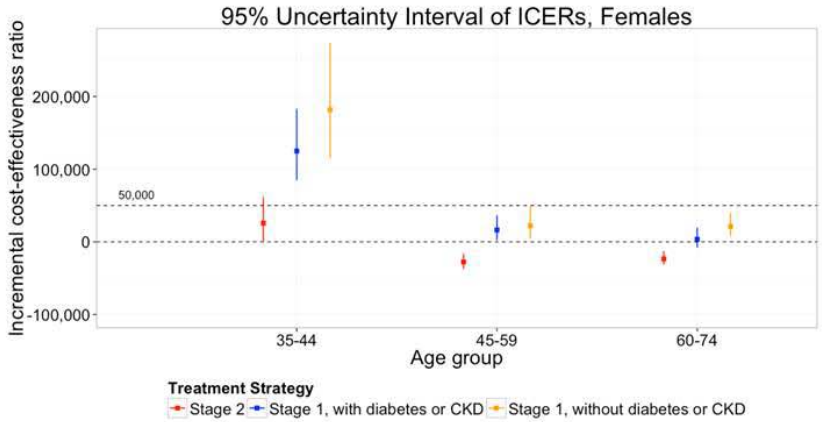


Appendix Figure S2. Incremental costs and effectiveness of treating to the target blood pressure in men and women, according to age group and targeted treatment group. Successive strategies add additional interventions; each strategy is compared with a prior, more effective strategy within the same age category. Base case represents a strategy of treating hypertension in all CVD patients with untreated hypertension.



Appendix Figure S3. Cost-effectiveness ratios and 95% intervals of results from the probabilistic (Monte Carlo) analysis, by age and major treatment group. All comparisons are with the base case of treating hypertension in all CVD patients with untreated hypertension. Note that all negative value incremental cost-effectiveness ratios are due to cost-savings divided by gained QALYs.





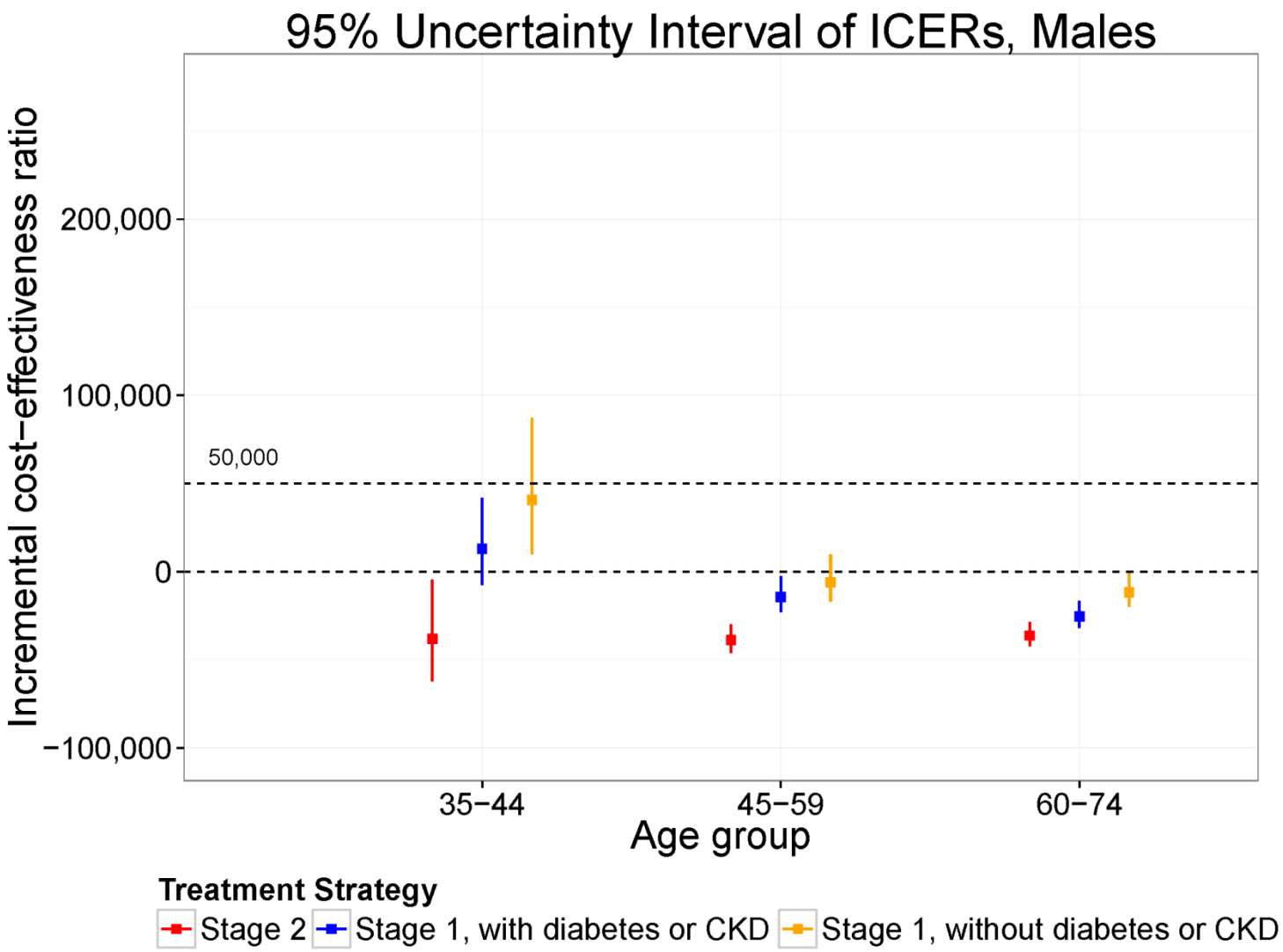
Percentage of ICERs below a given threshold, males

	35-44			45-59			60-74		
	Stage 2	DM/CKD	No DM/CKD	Stage 2	DM/CKD	No DM/CKD	Stage 2	DM/CKD	No DM/CKD
<$50,000	100.00	99.40	66.13	100.00	100.00	100.00	100.00	100.00	100.00
cost-saving	98.40	13.99	0.30	100.00	98.90	77.32	99.80	100.00	97.60

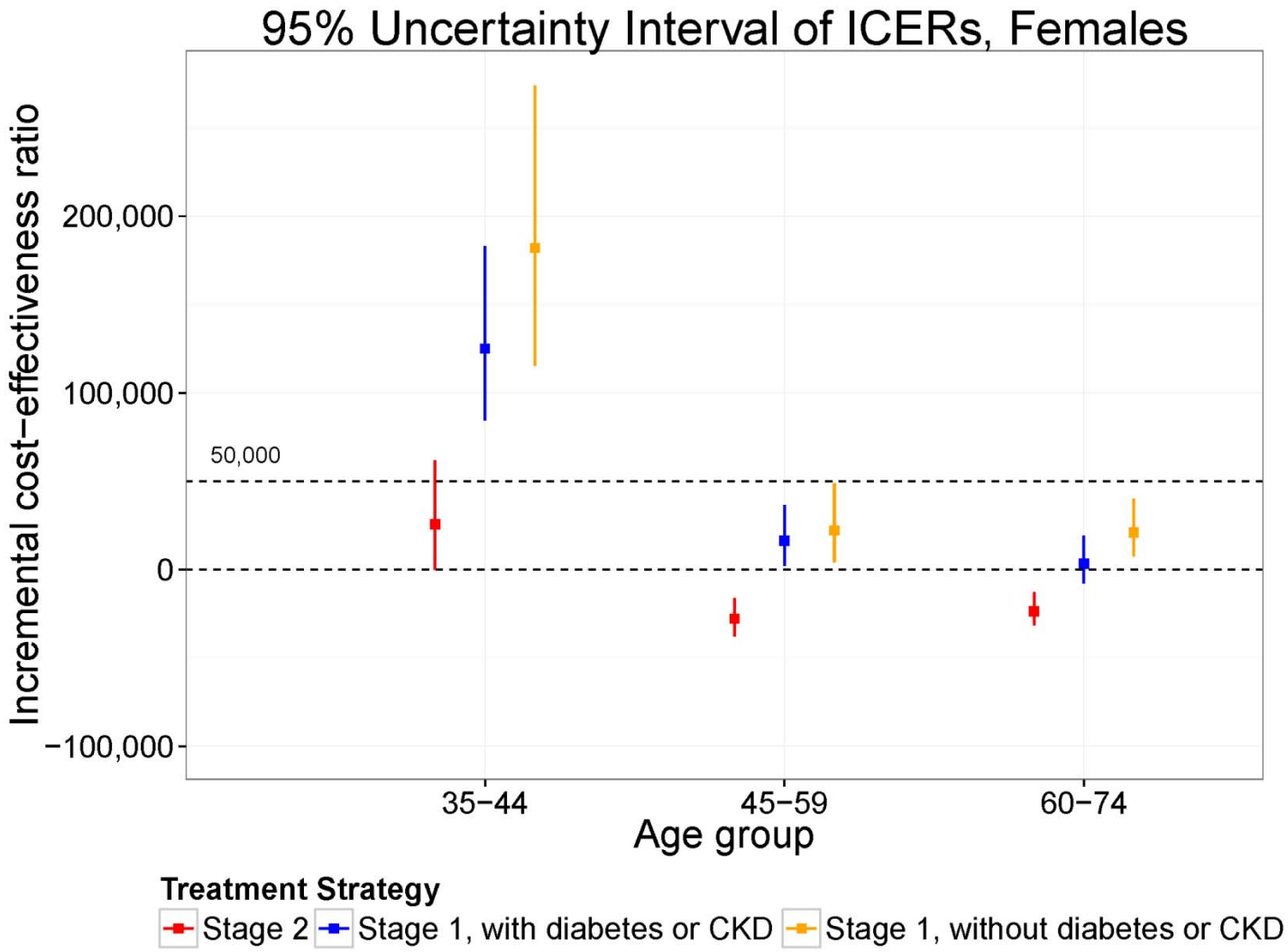
Percentage of ICERs below a given threshold, females

	35-44			45-59			60-74		
	Stage 2	DM/CKD	No DM/CKD	Stage 2	DM/CKD	No DM/CKD	Stage 2	DM/CKD	No DM/CKD
<$50,000	92.21	0.00	0.00	100.00	100.00	98.00	100.00	100.00	99.90
cost-saving	2.50	0.00	0.00	100.00	0.90	0.50	99.80	29.57	0.00

Panel A (Males) of Appendix Figure S3:



Panel B (Females) of Appendix Figure S3.



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