Supplementary Appendix

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

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Cost-Effectiveness of Intensive Versus Standard Blood Pressure Control

SUPPLEMENTARY APPENDIX

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SUPPLEMENTARY METHODS

Hypothetical Cohort

As specified in the analysis plan, the model was populated with a hypothetical cohort of 10,000 patients based on the characteristics of the population included in Systolic Blood Pressure Intervention Trial (SPRINT).[1] The rationale, design, and main results of SPRINT have been published elsewhere.[1-3] Briefly, The SPRINT eligibility criteria were: age ≥50 years; systolic blood pressure (SBP) of 130-180 mmHg on 0 or 1 antihypertensive medication class, 130-170 mmHg on up to 2 classes, 130-160 mmHg on up to 3 classes, 130-150 mmHg on up to 4 classes; and the presence of one or more high cardiovascular disease (CVD) risk conditions. High CVD risk conditions included history of clinical or subclinical cardiovascular disease other than stroke, estimated glomerular filtration rate (eGFR) of 20-59 ml/min/1.73m^2, 10-year risk for CVD ≥15% calculated using the Framingham risk score for general clinical practice, and age ≥75 years.[1,3] Participants were not eligible for SPRINT if they had any of the following: diabetes, a history of stroke, more than 1 gram/day of proteinuria, heart failure, were on dialysis, or had an eGFR <20 ml/min/1.73m^2. Detailed inclusion and exclusion criteria are listed in the SPRINT protocol.[2]

Microsimulation model

Patients in the simulation cycled uni-directionally through three different health states: 1) no CVD event, 2) post-CVD event, and 3) death. The post-CVD event state included each type of CVD event as well as the possibility of any combination of multiple CVD events. Within each health state, patients were at risk for three possible clinical events, 1) non-fatal or fatal CVD event, 2) non-fatal or fatal serious adverse event (SAE), or 3)

non-CVD death. Analyses were performed using TreeAge Pro 2016 (TreeAge Software, Inc, Williamstown, MA) and R (R version 3.1.0, Vienna, Austria).

Injurious falls were excluded as an SAE because no difference was found between the intensive and standard groups in SPRINT (intensive 7.1% vs. standard 7.1%, p=0.97).[1]

Rather than using a typical Markov model approach to time and model structure (i.e., discrete time intervals) with a half-cycle correction (Figure S1), the model was developed with a continuous time approach for assessing costs and outcomes. In this approach, three random draws from uniform time distributions, which corresponded to the order and timing of the three main events of interest (i.e., non-CVD mortality, SAEs, and CVD events), were performed every cycle in the model (Figure S2). Within each health state, the structure of the model contains six pathways, with each pathway containing a unique order of the main events of interest. This allowed for varying the time at which a patient became at risk for having each of the three events within a cycle and, in contrast to a traditional model structure, accounted for competing risks (Figure S2). Each cycle, the model ranked the value of each of the random time draws from smallest to largest. Then, the patient was assigned to the appropriate pathway corresponding to that order of risk.

The cumulative costs and benefits experienced in the model were calculated upon exiting the current cycle (i.e., either at 6 months if surviving all events or upon death). Costs, quality-adjusted life-years (QALYs), and life-years were calculated using

transition costs and benefits, and were based on the exact time of the fatal or non-fatal events. Chronic costs were truncated to discrete times as appropriate (e.g., prescription drug costs were incurred at monthly intervals because patients do not usually fill less than one month at a time). To calculate costs, QALYs, and life-years achieved, the survival time (person-years) was multiplied by the health state specific utility values.

A step-by-step explanation of the model process for a theoretical patient example is described below:

1. In the first 6-month cycle of the model, the following random values are drawn from the uniform time distributions: 0.25 for non-CVD death, 0.50 for CVD event, and 0.75 for SAE.
    a. The patient is first at risk of experiencing non-CVD death 25% of the way through the 6-month cycle (i.e., at 1.5 months).
    b. The patient survives and then becomes at risk of experiencing a CVD event 50% of the way through the 6-month cycle (i.e., at 3 months [1.5 months after the at risk for non-CVD death]).
    c. The patient survives and then becomes at risk of experiencing an SAE 75% of the way through the 6-month cycle (i.e., at 4.5 months [1.5 months after the at risk for a CVD event]).
    d. The patient survives and then exits the cycle at 6 months. Cumulative costs (i.e., treatment specific costs, chronic disease state costs, and acute event costs), QALYs, and life-years experienced are calculated at the time of exit by multiplying the percentage of time alive during current cycle by the appropriate values (e.g., 100% or 1.00*6 months = 0.5 life-years).

2. For the second 6-month cycle in the model, the following uniform distributions are drawn: 0.40 non-CVD death, 0.25 CVD event, and 0.65 SAE.
    a. The patient is first at risk of experiencing a CVD event 25% of the way through the 6-month cycle (i.e., 1.5 months).
    b. The patient experiences a fatal CVD-event and exits the cycle. The QALYs and life-years experienced are calculated by multiplying the percentage of time alive during current cycle (25% or 0.25*6 months = 1.5 months or 0.125 life-years). Chronic costs are calculated based on 2 months of costs (1.5 rounded up to nearest month). Acute costs are based on the type of CVD-event experienced (i.e., myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, or heart failure).
    c. The patient survived in the model for a total of 7.5 months or 0.625 life-years (cycle 1, 6 months * 1.0; cycle 2, 6 months * 0.25), and experienced 8 months of chronic healthcare costs and the costs associated with 1 acute hospitalization event.

Using this approach, the costs and QALYs were incurred for only the time spent in each state. Had the theoretical patient in the example experienced a non-fatal rather than a fatal CVD event, the time of the event would have represented the precise moment in the model when the patient would begin to experience chronic post-CVD event costs and utility associated with being in a post-CVD event state.

Systolic blood pressure (SBP) changes

Along with other patient characteristics, SBP was used to extrapolate outcomes from SPRINT over a lifetime. Two SBP values were randomly assigned to each patient at the start of the model: (1) baseline SBP which was derived from the distribution of baseline SBP values in the entire trial population and (2) treatment SBP which was derived from the distributions of the SBP for each arm at the end of SPRINT follow-up. It was assumed that treatment effect on SBP persisted throughout the first five years in all patients without an SAE, and continued beyond five years as long as the patient remained adherent to therapy. In addition, after the initial five year period, all patients began to experience age-related increases in SBP, which was derived from the Framingham Heart Study, regardless of adherence to treatment.[4]

In patients who experienced an SAE, regardless of whether it occurred before or after the initial 5 years, it was assumed that they stopped taking one antihypertensive medication and experienced an increase in SBP of 9.1 mmHg, which is equivalent to the mean SBP reduction with one standard dose antihypertensive.[5] If the SAE occurred during the first five years in the model, patients began to experience age-related increases in SBP at the time of the SAE.

It was assumed that all patients were adherent to their assigned treatment as observed in SPRINT during the first five years. However, if a patient became non-adherent to therapy after the initial five-year period, SBP was assumed to return to baseline SBP values and continued to experience age-related increases. The probability of being adherent to treatment was stratified by the number of anti-HTN medications a patient was receiving as derived from the literature.[6-8]

In addition to changes in medication due to SAEs, antihypertensive medication therapy changes occurred for increases in SBP. For every 10 mmHg increase in SBP above the SPRINT follow up treatment SBP, patients received one additional antihypertensive medication, up to a maximum of five medications.

Intervention costs

In the base-case, patients had four office visits per year in the intensive arm (two with lab monitoring) and three (one with lab monitoring) in the standard arm.[9-11] The cost of office visits and lab monitoring are described in Table S1, and were derived using CPT/HCPCS codes (Table S4) and estimates from the Centers for Medicare and Medicaid Services (CMS) Physician and Laboratory Fee Schedules.[12,13]

Chronic healthcare costs

Chronic non-CVD healthcare costs were stratified by age and sex and were applied during every cycle to account for the increased cost of survival with intensive SBP treatment.[10] All chronic costs attributable to CVD events were stratified by age and derived from the CDC Chronic Disease Cost Calculator.[14,15] No additional long-term costs were assigned to patients associated with the development of chronic kidney disease (CKD). However, if patients with CKD developed end-stage renal disease, then their chronic non-CVD costs were specific to ESRD as derived from published literature.[16]

Acute event costs

CVD events and SAEs were assumed to require an inpatient stay, the costs of which were derived using ICD-9 codes (Table S4) and estimates from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (HCUP).[17] Based on the clinical judgment and prior knowledge, it was assumed that SAEs would resolve within two weeks. The exception was acute kidney injury (AKI), which was assumed to resolve in the same time period as CVD events (i.e., 4 weeks).

To better understand the contributors to cost over time accrued over each cycle, we captured the individual components that made up total costs. These included treatment (i.e., antihypertensive medication costs, office visits, and laboratory monitoring), CVD events, SAEs, chronic CVD, and background direct medical costs.

Utilities

When patients had more than one chronic condition, rather than combining utilities, the condition with the lowest utility (most severe disability) was used.[18] Additionally, a one-time disutility of 0.1 was applied for CVD events and SAEs until the acute event resolved (i.e., 4 weeks for CVD events and AKI, 2 weeks for other SAEs).[10,19,20] For individuals entering the model with clinical CVD, we assigned the baseline utility of chronic MI. Main analyses relied on utility values estimated using the EuroQol five dimensions questionnaire (EQ-5D) in the U.S. Medical Expenditure Panel Survey.[21] Utility values were also directly measured in SPRINT using the EQ-5D.[22] The EQ-5D

was administered in SPRINT at the baseline visit and at the 12-month , 24-month, 36-month, and 48-month follow-up visits.[3] We used these values for in alternate Scenario 14 in Tables S5 and S10.

Probabilistic analyses

Probabilistic analyses examined joint uncertainty of parameter estimates in the model by running 1,000 simulations, each taking random draws from the pre-specified uncertainty distributions of all input parameters. Costs used a gamma distribution, estimates based on proportions (e.g., probability of SAEs, probability of CVD events) used beta distributions, and utility values used beta distributions. As the model was run using microsimulation, the probabilistic analyses consisted of 1,000 and 5,000 iterations, that each contained 10,000 simulated patients individually run through the model. We used these results to determine uncertainty intervals around cost and effectiveness estimates using the 2.5 and 97.5 percentiles. We used willingness-to-pay (WTP) thresholds between $50,000 and $150,000/QALY to determine the probability of intensive SBP treatment being cost-effectiveness from the probabilistic analyses.[23] While WTP thresholds of $50,000-$100,000/QALY are commonly accepted in the US, some have argued for thresholds of $150,000/QALY or higher.[24,25] Thus, we explored a range of WTP values from $50,000-$150,000/QALY.

Persistence of treatment effect, medication adherence, and other alternate scenario analyses

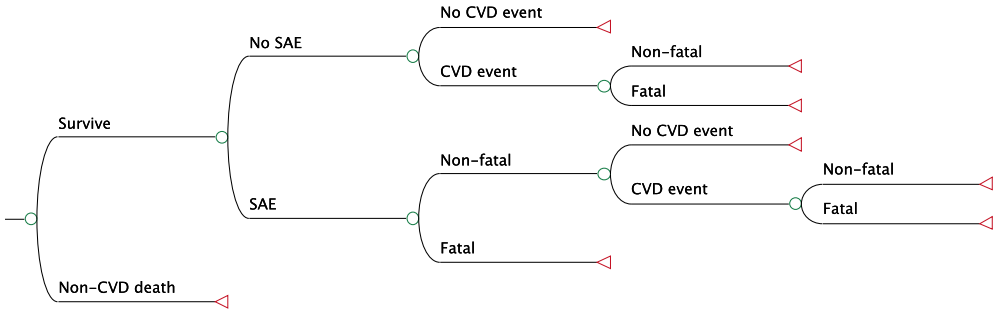
Several key assumptions were required in order to extrapolate short-term clinical trial results beyond the trial period, and we performed alternate scenario analyses to test these assumptions (Table S2, S3, and S5). We also performed subgroup analyses using probabilistic analyses and the summary treatment effects for the subgroups reported in SPRINT.[1] Subgroups examined, included baseline age above or below 75 years, sex, baseline CKD, black or non-black race, and baseline CVD history. For subgroup analyses, the computer simulation model assembled a full sample of 10,000 patients who met the subgroup definition.

Medication Adherence Measured Directly in SPRINT

It was assumed that all patients were adherent to their assigned treatment as observed in SPRINT during the first five years. Medication adherence was measured in SPRINT using the 8-item Morisky Medication Adherence Scale (MMAS-8) which is an eight question self-reported instrument that has proven to be a valid and reliable assessment tool for assessing antihypertensive medication adherence.[26,27] The MMAS-8 was administered in SPRINT at the baseline visit and at the 12-month and 48-month follow-up visits.[3] The MMAS-8 is a self-reported questionnaire intended to measure medication adherence by providing information about behavioral and psychological factors that may act as barriers to medication adherence. The MMAS-8 is scored as an ordinal measure with scores ranging from 0 to 8. It is categorized with a score of <6 indicating ‘‘low adherence,’’ 6 to <8 ‘‘medium adherence,’’ and 8 ‘‘high adherence’’ based on previously published definitions.[26-28] We used these values for Scenario 10 in Tables S5 and S10.

SUPPLEMENTARY FIGURES

Figure S1: Example of a conventional model structure for clinical events within a given cycle

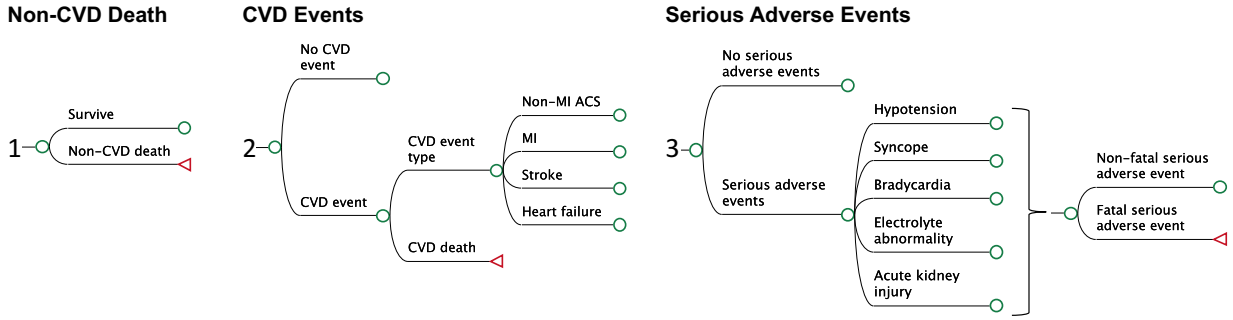


This figure shows a conventional model structure that does not allow the order of events to change within a given cycle. In the example above, if a patient had a non-CVD death they would not be able to experience an SAE or CVD event in that cycle.

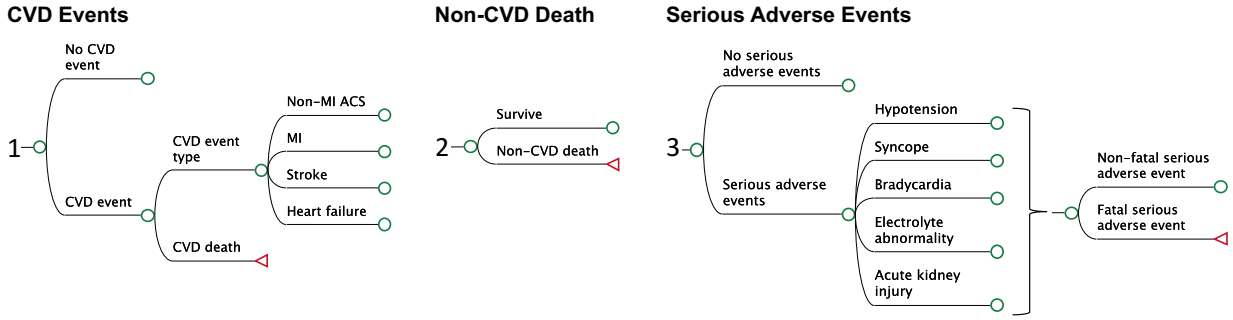
CVD – Cardiovascular disease, SAE – Serious adverse event

Figure S2: Three examples to show the flexible, continuous time approach used in our model structure

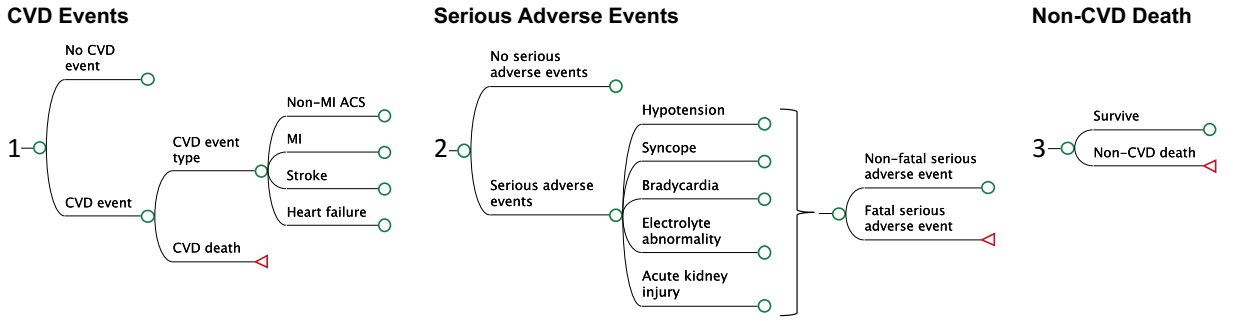
A) Order of risk: non-CVD death, CVD event, SAE



B) Order of risk: CVD event, non-CVD death, SAE



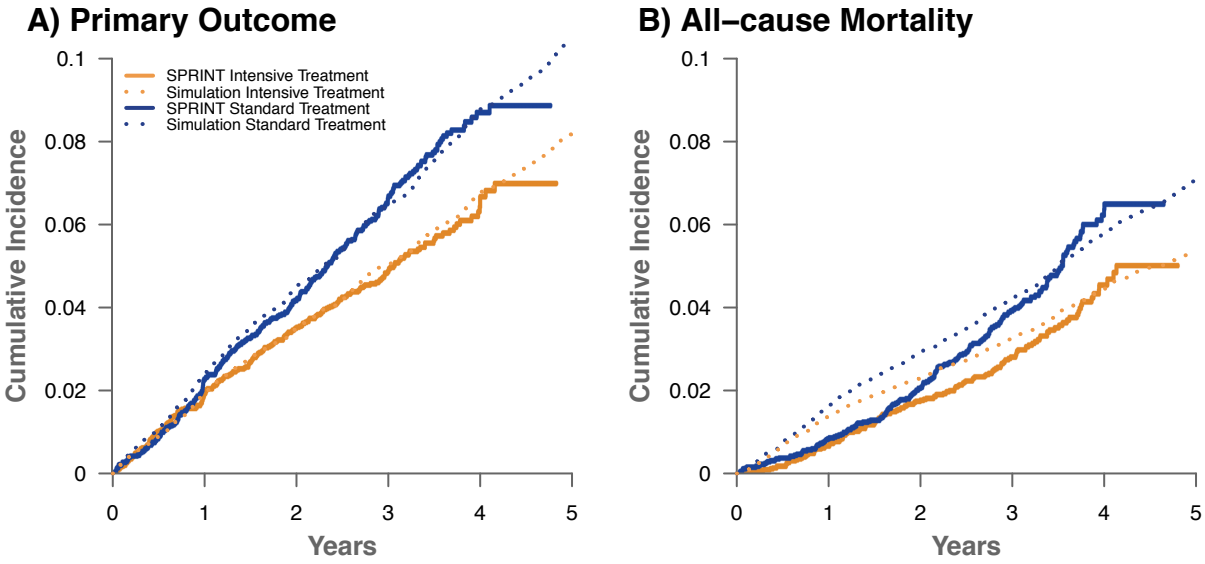
C) Order of risk: CVD event, SAE, non-CVD death



This figure shows three of the six potential pathways a patient could experience within a given cycle. With this approach, patients were randomly assigned the potential time at which they were at risk of experiencing events and thus order of the model structure. In contrast to Figure S1, by using this flexible approach, patients could potentially experience both an SAE and a non-CVD death in the same cycle. Additionally, the events of interest could occur at any time during the cycle (continuous time as opposed to discrete time). A detailed narrative description of these hypothetical event sequences is provided on pages 6 and 7 of the Supplementary Methods.

CVD – Cardiovascular disease, SAE – Serious adverse event

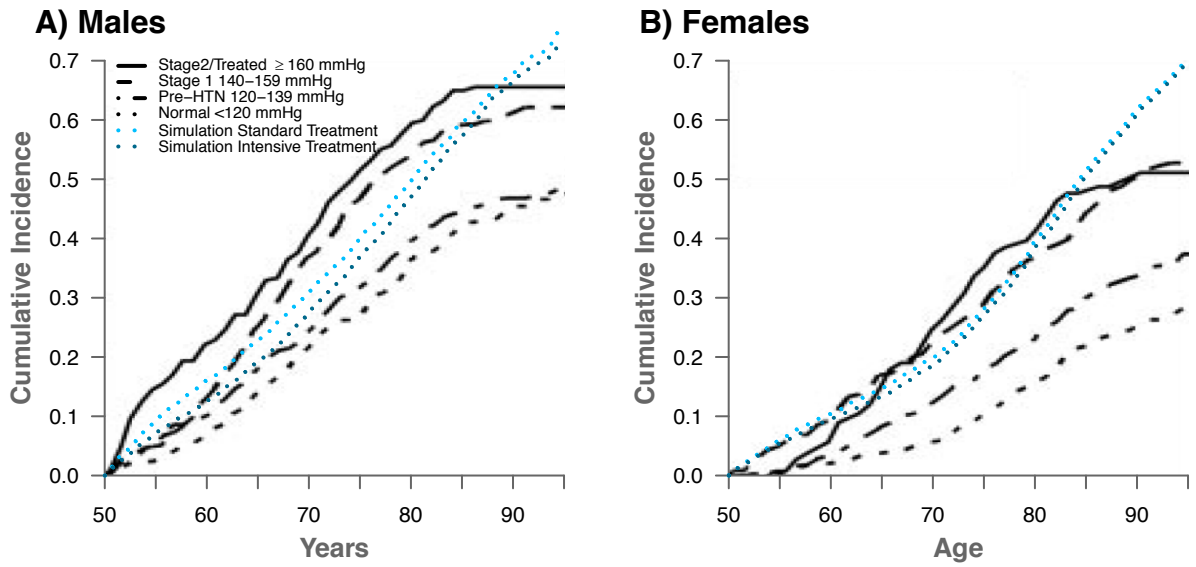
Figure S3: Comparison of the cumulative incidence of the SPRINT primary outcome and all-cause mortality observed in SPRINT to the base-case scenario of the simulation model



The SPRINT primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

SPRINT – Systolic Blood Pressure Intervention Trial

Figure S4: Comparison of the cumulative incidence of the simulation model primary outcome (excluding heart failure) to the Framingham Heart Study cohorts

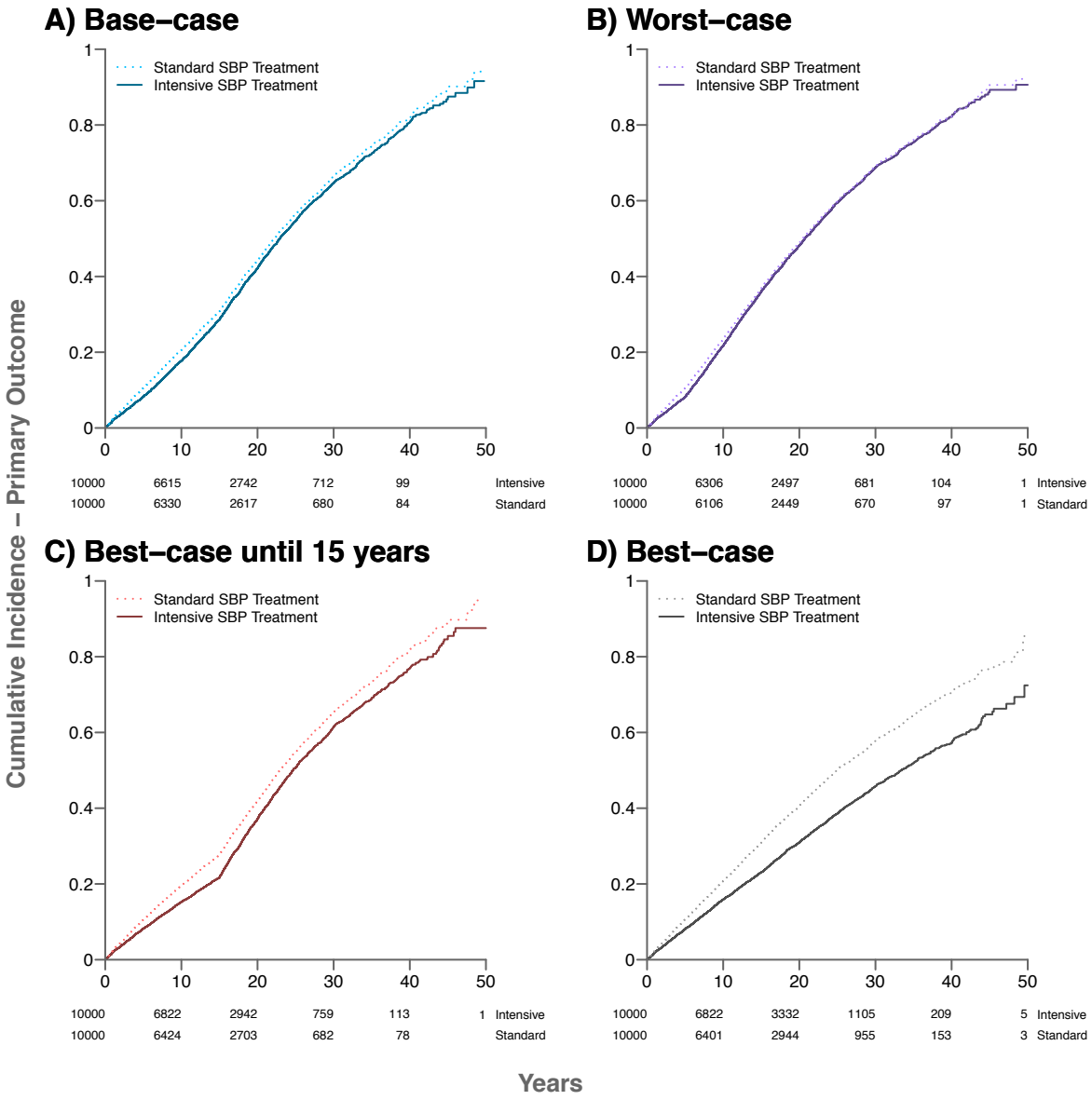


This figure shows the cumulative incidence of the SPRINT primary outcome (excluding heart failure) from the microsimulation model and cumulative incidence of CVD events adjusted for the competing risk of death for men and women according to individual risk factor strata at 50 years of age from Lloyd-Jones et al. using data from the Framingham Heart Study cohorts.[29] The simulation model used the base-case assumptions and was populated with the characteristics of the Framingham Heart Study participants. In Lloyd-Jones et al., atherosclerotic CVD events were defined by the occurrence of myocardial infarction, coronary insufficiency, death resulting from coronary heart disease, angina pectoris, atherothrombotic stroke, intermittent claudication, or other cardiovascular death.[29] Thus, the model primary outcome was based on the SPRINT outcomes, but was modified to exclude heart failure for better comparison to the Framingham Heart Study cohorts.

Original figures reproduced with permission from Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 2006;113:791-8.

HTN – Hypertension.

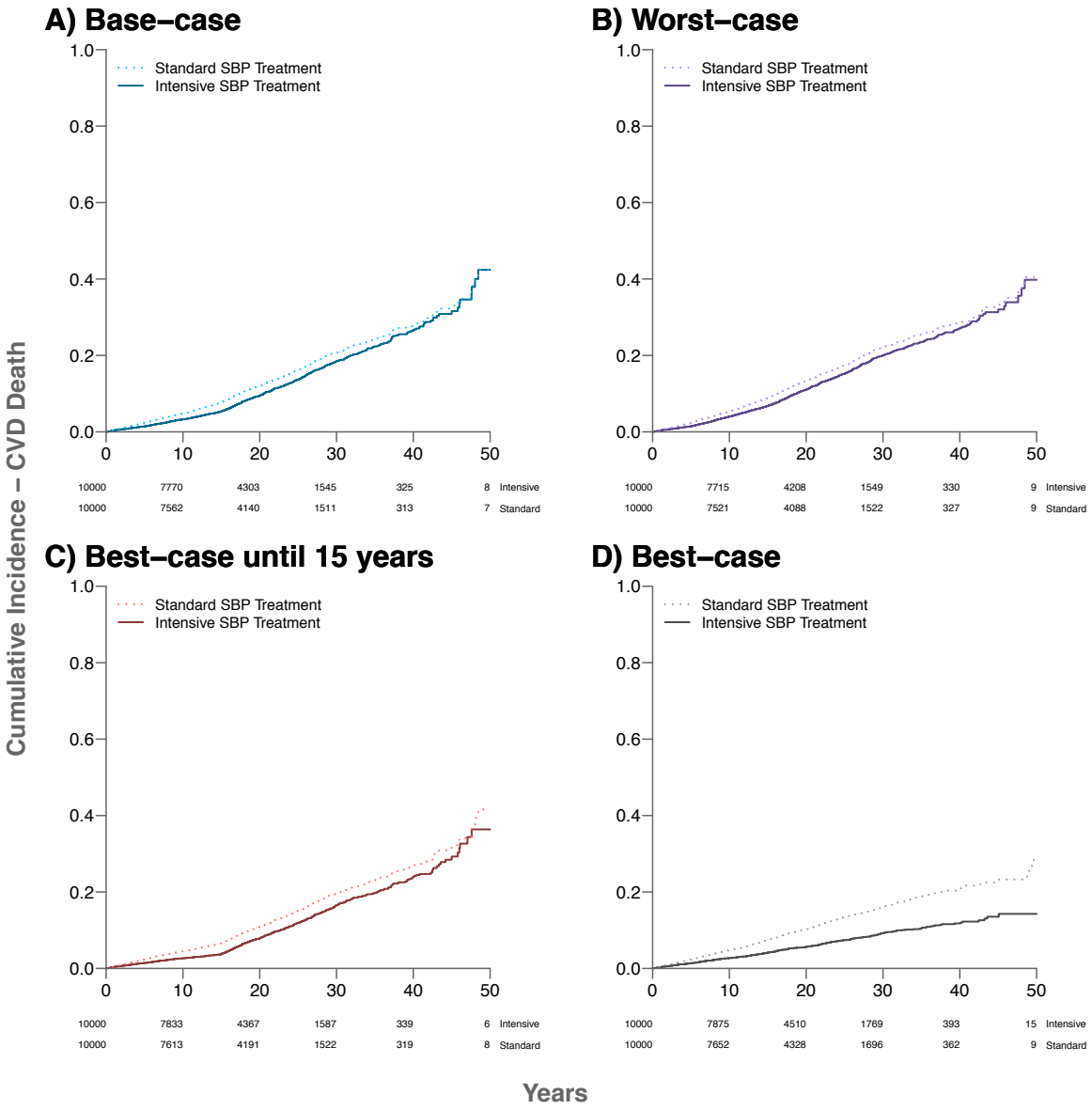
Figure S5: Comparison of cumulative incidence of the SPRINT primary outcome across different post-trial adherence and treatment effect scenarios



Figures show the cumulative incidence of the first SPRINT primary outcome over time during the simulation. The four different post-trial adherence scenarios are shown: Panel A is the base-case scenario, Panel B is the worst-case scenario, Panel C is best-case until 15 years scenario, and Panel D is the best-case scenario. The y-axis represents the cumulative incidence of the primary outcome and the x-axis represents the time since randomization. The text below the x-axis indicates the number of patients still at risk at that time. The SPRINT primary composite outcome was the first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes.

SBP – Systolic blood pressure, SPRINT – Systolic Blood Pressure Intervention Trial

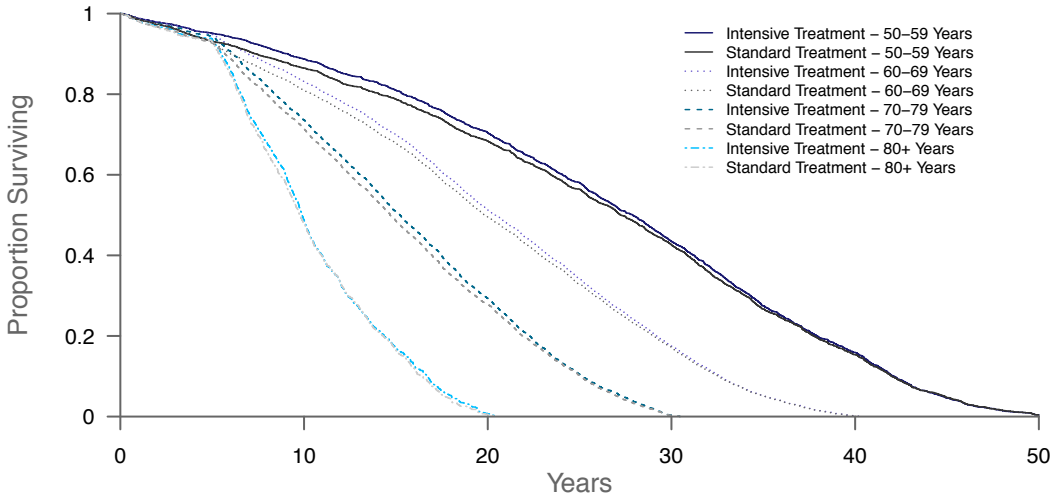
Figure S6: Comparison of cumulative incidence of cardiovascular disease death across different post-trial adherence and treatment effect scenarios



Figures show the cumulative incidence of CVD death over time during the simulation. The four different post-trial adherence scenarios are shown: Panel A is the base-case scenario, Panel B is the worst-case scenario, Panel C is best-case until 15 years scenario, and Panel D is the best-case scenario. The y-axis represents the cumulative incidence of CVD death and the x-axis represents the time since randomization. The text below the x-axis indicates the number of patients still at risk at that time.

CVD – Cardiovascular disease, SBP – Systolic blood pressure

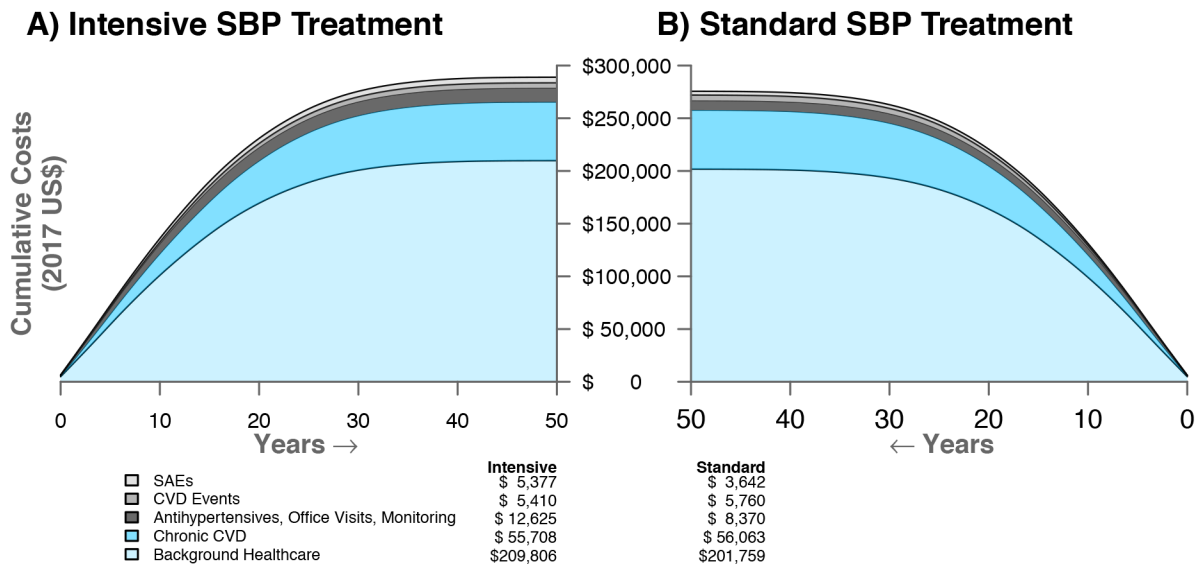
Figure S7: All-cause mortality survival curves, stratified by baseline age category, from the base-case analysis



Intensive Treatment	2023	1795	1425	879	322	8	50–59 Years
	3756	3122	1929	657	3		60–69 Years
	3208	2360	942	9			70–79 Years
	1013	493	7				80+ Years
Standard Treatment	2023	1749	1383	862	311	7	50–59 Years
	3756	3040	1860	641	2		60–69 Years
	3208	2288	892	8			70–79 Years
	1013	485	5				80+ Years

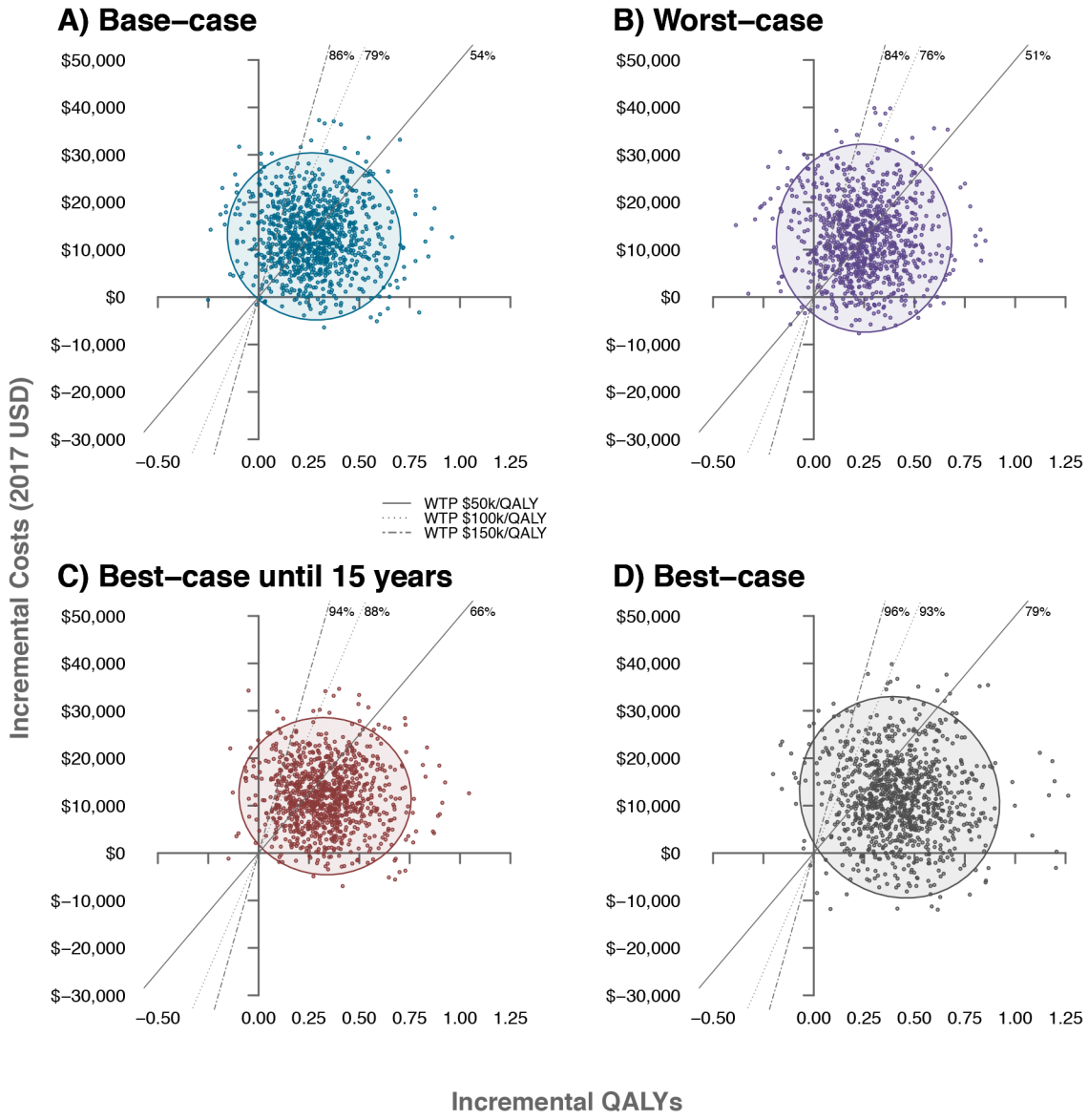
Figure shows the overall survival during the simulation for the base-case scenario (i.e., post-trial decay in adherence and treatment effects) stratified by baseline age. The text below the x-axis indicates the number of patients still at risk at that time for each treatment arm by baseline age category.

Figure S8. Cumulative incremental direct medical costs by type with intensive (Panel A) and standard SBP (Panel B) treatment over time



CVD – Cardiovascular disease, SAEs – Serious adverse events, SBP – Systolic blood pressure

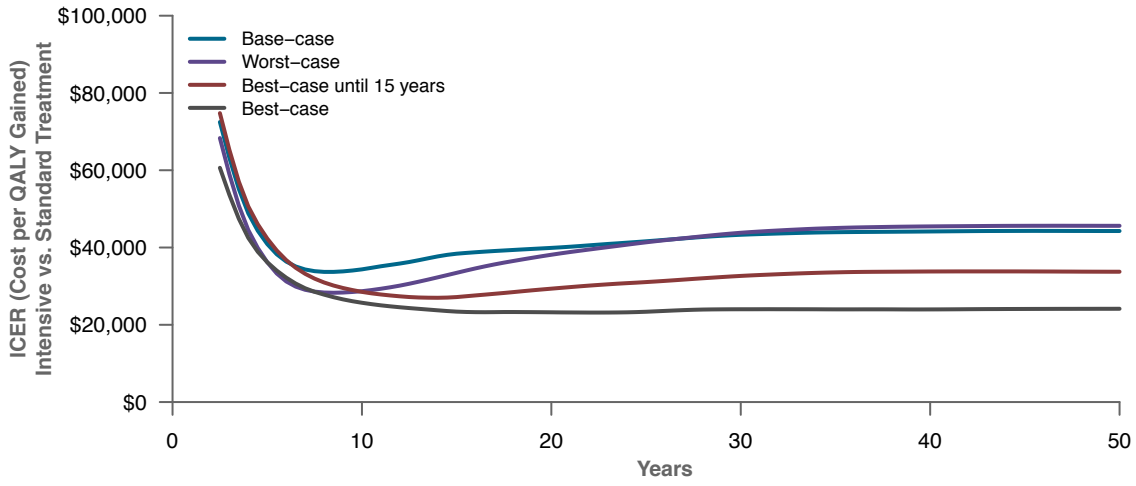
Figure S9: Results of the probabilistic analyses as shown on a cost-effectiveness scatter plot



The figure shows the cost-effectiveness scatterplot for each of the four post-trial period treatment effects and adherence scenarios. The x-axis is the mean difference in cumulative QALYS between the intensive and standard treatments. The y-axis is the mean difference in cumulative costs between intensive and standard treatments. The three WTP lines drawn on each plot show the $50,000, $100,000, and $150,000/QALY WTP thresholds. The percentages shown next to each line are the proportion of simulations resulting in intensive treatment being cost-effective at that WTP threshold (proportion of iterations below the line). The colored oval shows the 95% uncertainty interval for the joint distribution of incremental costs and QALYs.

USD – United States dollars, QALY – uality-adjusted life-year, WTP – Willingness-to-pay.

Figure S10: Comparison of the incremental cost-effectiveness ratio over time between the four post-trial adherence and treatment effect scenarios



The figure shows the impact changing the model time horizon from 3 years to 50 years has on the ICER.

ICER – Incremental cost-effectiveness ratio, QALY – Quality-adjusted life-year

Figure S11: Results of the non-probabilistic one-way sensitivity analyses

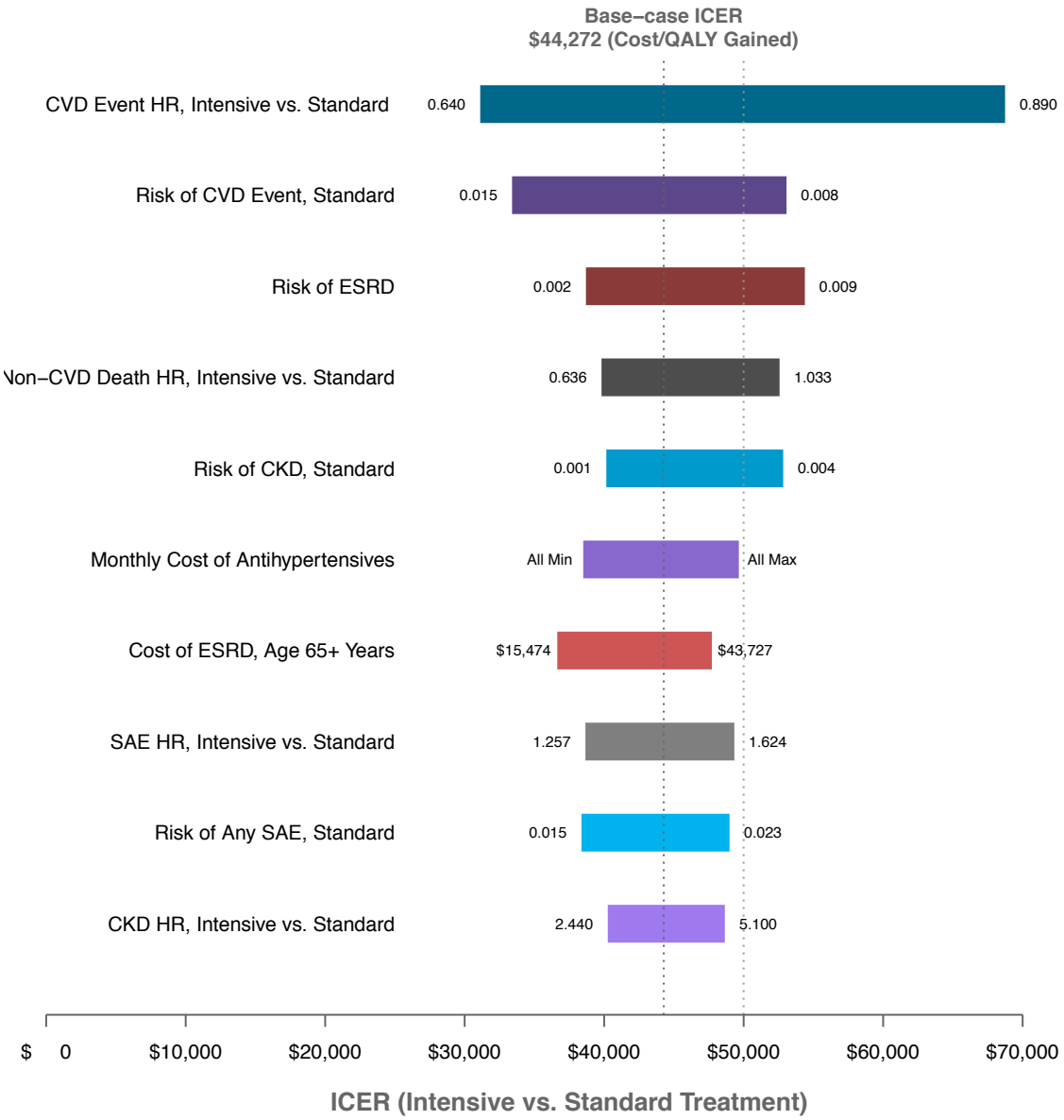


Figure shows the results of the one-way sensitivity analyses where model parameters were varied across a range of plausible values to see the impact on the ICER. The ten parameters to which the model was most sensitive are shown; other parameters changed the ICER by <$10,000/QALY gained and none caused the ICER to increase to >$50,000/QALY gained. Plausible ranges were preferentially derived from reported 95%CIs or ranges, or calculated 95%CIs using variance estimates as available. The small numbers/text on the outside of each bar indicate the value of that parameter that resulted in the lowest and highest ICERs.

CI – Confidence interval, CKD – Chronic kidney disease, CVD – Cardiovascular disease, ESRD – End-stage renal disease, HR – Hazard ratio, ICER – Incremental cost-effectiveness ratio, QALY – Quality-adjusted life-year, SAE – Serious adverse event.

Figure S12: Results of the non-probabilistic threshold analysis of serious adverse events in the post-trial period (Scenario 20)

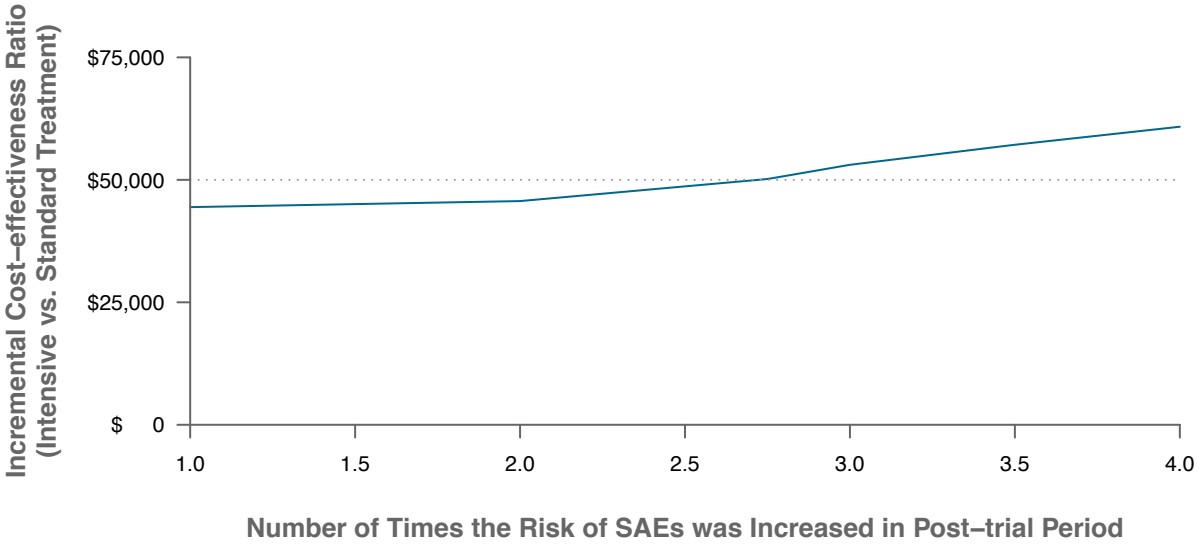
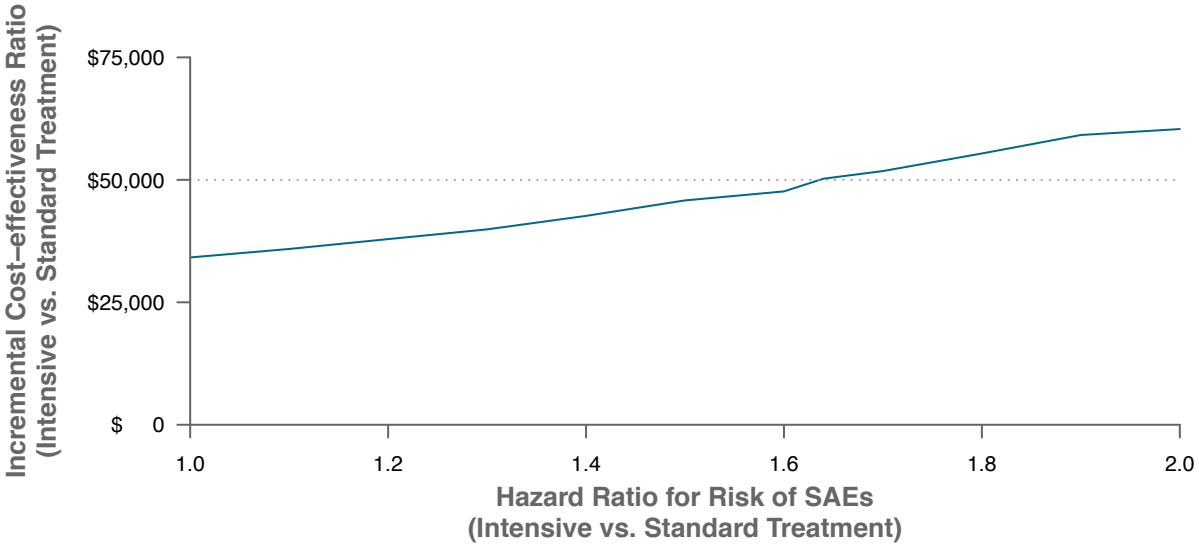


Figure shows the results of the threshold analysis that showed the risk of SAEs in the post-trial period needed to be increased by 2.75 times for intensive SBP treatment to no longer be cost-effective at a $50,000/QALY willingness-to-pay threshold.

QALY – Quality-adjusted life-year, SAE – Serious adverse event

Figure S13: Results of the non-probabilistic threshold analysis of intensive vs. standard treatment serious adverse event hazard ratio (Scenario 21)



The figure shows the results of the threshold analysis that determined the hazard ratio (intensive vs. standard treatment) for risk of any SAE (i.e., hypotension, bradycardia, electrolyte abnormality, syncope, or acute kidney injury) needed to be 1.64 for intensive SBP treatment to no longer be cost-effective at a $50,000/QALY willingness-to-pay threshold.

QALY – Quality-adjusted life-year, SAE – Serious adverse event, SBP – Systolic blood pressure.

SUPPLEMENTARY TABLES

Table S1. Model input values, ranges, and distributions

Parameter	Source	Base-Case Value	SD	Min	Max	Distribution
Patient Characteristics						
Overall Baseline Characteristics	Derived from overall SPRINT cohort[1]					
Age (years), mean		67.90	9.40			Normal
Female Sex (%)		35.59%				
Black (%)		31.48%				
Current smoker (%)		13.25%				
CKD (%)		28.26%				
Clinical CVD (%)		16.68%				
Baseline SBP (mmHg), mean		139.70	15.60			Normal
Baseline DBP (mmHg), mean		78.10	11.90			Normal
Total cholesterol (mg/dL), mean		190.10	41.10			Normal
HDL-C (mg/dL), mean		52.80	14.50			Normal
Baseline number of antihypertensive medications, mean		1.80	1.00			Normal

Parameter	Source	Base-Case Value	SD	Min	Max	Distribution
Number of Antihypertensive Medications Received as Part of Intervention, mean	SPRINT[1]					
Intensive		2.70	1.20	-	-	Normal
Standard		1.80	1.10	-	-	Normal
Blood Pressure						
SBP Achieved Due to Intervention (mmHg), mean	SPRINT[1]					
Intensive		121.50	1.71	-	-	Normal
Standard		134.60	1.86	-	-	Normal
Change in SBP Per Cycle as Patients Age	Franklin et al.[4]	0.44	0.07	0.31	0.58	Normal
Probabilities						
If CVD event occurred, probability it was:	SPRINT[1]					
Myocardial infarction						
Intensive		37.16%	2.97%	31.71%	43.37%	Beta
Standard		35.58%	2.64%	30.73%	41.08%	Beta
Unstable angina						
Intensive		15.33%	2.23%	11.63%	20.41%	Beta

Parameter	Source	Base-Case Value	SD	Min	Max	Distribution
Standard		12.27%	1.82%	9.27%	16.45%	Beta
Stroke						
Intensive		23.75%	2.62%	19.17%	29.48%	Beta
Standard		21.47%	2.27%	17.50%	26.41%	Beta
Heart failure						
Intensive		23.75%	2.62%	19.17%	29.48%	Beta
Standard		30.67%	2.54%	26.06%	36.04%	Beta
If SAE Occurred, Probability it was:	SPRINT[1]					
Hypotension						
Intensive		19.60%	1.40%	17.07%	22.55%	Beta
Standard		17.29%	1.63%	14.41%	20.12%	Beta
Syncope						
Intensive		20.22%	1.41%	17.65%	23.20%	Beta
Standard		21.00%	1.75%	17.86%	24.01%	Beta
Bradycardia						
Intensive		12.90%	1.18%	10.82%	15.46%	Beta

Parameter	Source	Base-Case Value	SD	Min	Max	Distribution
Standard		15.43%	1.56%	12.71%	18.15%	Beta
Electrolyte abnormality						
Intensive		21.96%	1.46%	19.30%	25.01%	Beta
Standard		23.98%	1.84%	20.65%	27.11%	Beta
Acute kidney injury						
Intensive		25.31%	1.53%	22.49%	28.49%	Beta
Standard		22.30%	1.79%	19.08%	25.37%	Beta
Probability SAE was fatal	H-CUP[17]					
Hypotension		1.02%	0.03%	0.96%	1.09%	Beta
Syncope		0.18%	0.01%	0.16%	0.20%	Beta
Bradycardia		0.90%	0.02%	0.85%	0.95%	Beta
Electrolyte abnormality		1.15%	0.02%	1.12%	1.19%	Beta
Acute kidney injury		3.14%	0.02%	3.10%	3.19%	Beta
*Medication Adherence After First Five Years**						
Number of antihypertensive medications						
0 (Assumed to be lifestyle modifications)	Jones et al.[7], Xu et al.[8]	69.56%	12.74%	35.03%	85.98%	Beta

Parameter	Source	Base-Case Value	SD	Min	Max	Distribution
1	Iskedjian et al.[6]	91.40%	2.20%	89.24%	93.27%	Beta
2	Iskedjian et al.[6]	87.10%	2.90%	85.36%	88.72%	Beta
3+	Iskedjian et al.[6]	83.20%	3.50%	82.01%	82.01%	Beta
Costs (2017 USD)						
Acute CVD Event Costs (Per Episode)	H-CUP[17]					
Unstable angina						
50-64		$7,254	$440	$6,592	$8,318	Gamma
65-84		$7,442	$382	$6,563	$8,060	Gamma
≥85		$5,618	$457	$5,345	$7,137	Gamma
Myocardial infarction						
50-64		$22,134	$3,837	$14,093	$29,135	Gamma
65-84		$22,004	$4,101	$13,983	$30,058	Gamma
≥85		$13,903	$3,753	$8,138	$22,849	Gamma
Heart failure						
50-64		$11,179	$1,145	$11,164	$15,653	Gamma
65-84		$10,218	$1,150	$10,216	$14,725	Gamma

Parameter	Source	Base-Case Value	SD	Min	Max	Distribution
≥85		$8,744	$1,370	$5,805	$11,179	Gamma
Stroke						
50-64		$16,248	$14,423	$5,624	$62,162	Gamma
65-84		$12,478	$10,075	$5,371	$44,865	Gamma
≥85		$10,119	$5,601	$6,267	$28,222	Gamma
Fatal CVD event						
50-64		$18,597	$5,081	$11,705	$31,622	Gamma
65-84		$17,157	$4,483	$11,309	$28,887	Gamma
≥85		$11,753	$3,333	$7,482	$20,547	Gamma
SAE Costs (Per Episode)	H-CUP[17]					
Hypotension						
50-64		$7,296	$817	$7,074	$10,274	Gamma
65-84		$7,331	$237	$7,160	$8,086	Gamma
≥85		$6,607	$182	$5,880	$7,099	Gamma
Syncope						
50-64		$6,593	$225	$6,152	$7,033	Gamma

Parameter	Source	Base-Case Value	SD	Min	Max	Distribution
65-84		$6,801	$225	$6,361	$7,241	Gamma
≥85		$6,662	$182	$6,304	$7,021	Gamma
Bradycardia						
50-64		$10,807	$2,165	$8,905	$17391	Gamma
65-84		$12,372	$1,952	$9,126	$16,776	Gamma
≥85		$11,941	$1,885	$8,450	$15,841	Gamma
Electrolyte abnormality						
50-64		$7,139	$1,207	$4,850	$9,582	Gamma
65-84		$7,144	$1,270	$4,923	$9,901	Gamma
≥85		$6,572	$1,529	$3,080	$9,072	Gamma
AKI						
50-64		$10,219	$2,676	$6,692	$17,183	Gamma
65-84		$9,862	$2,459	$7,290	$16,929	Gamma
≥85		$8,542	$2,005	$6,569	$14,429	Gamma
Incremental Long-term Post-CVD Event Costs (Per Cycle)	CDC Chronic Disease Cost Calculator[14,15]					

Parameter	Source	Base-Case Value	SD	Min	Max	Distribution
Post-MI (assumed to be cost of CHD)						
50-64		$3,013	$220	$2,597	$3,460	Gamma
≥65		$5,184	$379	$4,470	$5,952	Gamma
Post-unstable angina (assumed to be cost of CHD)						
50-64		$3,013	$220	$2,597	$3,460	Gamma
≥65		$5,184	$379	$4,470	$5,952	Gamma
Heart failure						
50-64		$3,698	$268	$3,229	$4,278	Gamma
≥65		$6,364	$461	$5,554	$7,361	Gamma
Acute stroke rehabilitation costs (first year post-stroke, 6-month cycle cost shown)	Moran et al.[10]	$8,705	$1,088	$6,529	$10,881	Gamma
Post-stroke (per cycle cost in subsequent years)	CDC Chronic Disease Cost Calculator[14,15]					
50-64		$5,334	$331	$4,836	$6,137	Gamma
≥65		$10,474	$712	$9,456	$12,247	Gamma
Non-CVD Background Costs (experienced by all simulated individuals; per cycle)	Moran et al.[10]	**Male**	**SD**	**Female**	**SD**	

Parameter	Source	Base-Case Value	SD	Min	Max	Distribution
50-54		$2,096	$262	$3,040	$380	Gamma
55-64		$2,793	$349	$4,374	$547	Gamma
65-74		$4,153	$519	$5,371	$671	Gamma
75-84		$6,285	$786	$8,009	$1,001	Gamma
≥85		$12,048	$1,506	$14,054	$1,757	Gamma
Long-term ESRD Costs (Used as Non-CVD background costs after developing ESRD)	USRDS[16]	$34,933	$7,207	$15,474	$43,727	Gamma
Medication Costs (Monthly)						
Number of antihypertensive medications	SPRINT[1], RED BOOK[30]					
0		$0	-	-	-	-
1		$14	$18	$3	$83	Gamma
2		$31	$24	$7	$137	Gamma
3		$50	$27	$11	$167	Gamma
4		$70	$27	$18	$174	Gamma
5		$95	$29	$28	$179	Gamma
Office Visit Costs (Per Episode)						

Parameter	Source	Base-Case Value	SD	Min	Max	Distribution
Office visit	CMS Physician Fee Schedule[12]	$111	$8	$91	$140	Gamma
Number of office visits per year[31,32]						
Intensive		4				
Standard		3				
Electrolyte monitoring	CMS Lab Fee Schedule[13]	$11	$1	$9	$12	Gamma
Number of times monitored per year						
Intensive		2				
Standard		1				
Utilities						
Model Comorbidities	Sullivan et al.[21]					
Hypertension		1.00	-	-	-	-
Stable angina		0.70	0.08	0.52	0.83	Beta
Post-myocardial infarction		0.70	0.07	0.58	0.84	Beta
Heart failure		0.64	0.10	0.44	0.81	Beta
Post-stroke		0.65	0.09	0.46	0.82	Beta

Parameter	Source	Base-Case Value	SD	Min	Max	Distribution
ESRD		0.65	0.08	0.51	0.82	Beta
Acute Event Disutility						
CVD events (1 month in duration)	Moran et al.[10], King et al.[19], Yao et al.[20]	-0.10	0.03	-0.08	-0.13	Beta
Acute kidney injury (1 month in duration)	Assumed same as acute CVD event	-0.10	0.03	-0.08	-0.13	Beta
Other SAEs (0.5 months in duration)	Assumed same as acute CVD event but shorter in duration	-0.10	0.03	-0.08	-0.13	Beta

Minimum and maximum values were preferentially derived from reported 95% confidence intervals or ranges, or calculated 95% confidence intervals using variance estimates as available.

CDC – Centers for Disease Control and Prevention, CHD – Coronary heart disease, CKD – Chronic kidney disease, CMS – Centers for Medicare and Medicaid Services, CVD – Cardiovascular disease, DBP – Diastolic blood pressure, ESRD – End-stage renal disease, H-CUP – Healthcare Cost and Utilization Project, HDL-C – High density lipoprotein cholesterol, SAE – Serious adverse event, SBP – Systolic blood pressure, SD – Standard deviation, SPRINT – Systolic Blood Pressure Intervention Trial, USD – United States dollars, USRDS – United States Renal Data System.

Table S2: Key assumptions regarding risk of clinical events in the four post-trial period adherence and treatment effect scenarios

	First 5 years (planned SPRINT follow up)	After the first 5 years (model projection of SPRINT results)			
				Probability of events	
Scenario	**All patients**	**Adherence definition**	***SBP and anti-HTN medications***	**Adherent patients**	**Non-adherent**
Base-case	*Adherence:* • All patients adherent to therapy *Event Probabilities:* • *SAEs:* as observed in SPRINT • *First CVD event:* as observed in SPRINT • *Repeat CVD event:* derived from Pooled Cohort risk equations • *Non-CVD death:* as observed in SPRINT	• Intermittently adherent based on number of anti-HTN meds • All patients permanently non-adherent after first 15 years	*Adherent* • SPRINT treatment SBP persists *Non-Adherent* • SBP returns to baseline value (no reduction) *All Patients* • SBP increases over time (0.89 mmHg/year)[4] • 1 anti-HTN med added per each 10 mmHg increase in SBP over goal • 9.1 mmHg reduction in SBP/additional med added[5] • 5 anti-HTN med max • If patient experiences SAE, 1 anti-HTN removed and 9.1 mmHg increase in SBP[5]	*SAEs* • As observed in SPRINT *First CVD event* • As observed in SPRINT *Repeat CVD event* • Derived from Pooled Cohort[33] *Non-CVD death* • Derived from CDC life-tables[34]	*SAEs* • As observed in standard arm of SPRINT *First CVD event* • Derived from Pooled Cohort[33] *Repeat CVD event* • Derived from Pooled Cohort[33] *Non-CVD death* • Derived from CDC life-tables[34]
Worst-case	• Same as base-case	• All patients permanently non-adherent at 5 years	• Same as base-case	• N/A (all patients non-adherent)	• Same as base-case

Best-case until 15 years	*Event Probabilities:* • *SAEs:* as observed in SPRINT • *First or repeat CVD event:* as observed in SPRINT • *Non-CVD death:* as observed in SPRINT	• All patients adherent for first 15 years • All patients permanently non-adherent after first 15 years	• Same as base-case	• First CVD event, SAEs, and Non-CVD Death same as base-case *Repeat CVD event* • First 15 years, as observed in SPRINT	• Same as base-case
Best-case	*Event Probabilities:* • *SAEs:* as observed in SPRINT based on age, <75 vs. ≥75 years • *First or repeat CVD event:* as observed in SPRINT based on age, <75 vs. ≥75 years • *Non-CVD death:* as observed in SPRINT based on age, <75 vs. ≥75 years	• All patients over their entire lifetime	• Same as base-case	*SAEs* • As observed in SPRINT based on age, <75 vs. ≥75 years *First or repeat CVD event:* • As observed in SPRINT based on age, <75 vs. ≥75 years *Non-CVD death* • Derived from CDC life-tables[34]	• N/A (all patients adherent)

Anti-HTN – antihypertensive, CDC – Centers for Disease Control and Prevention, CVD – cardiovascular disease, mmHg – Millimeters of mercury, N/A – not applicable, SAE – serious adverse event, SBP – systolic blood pressure, SPRINT – Systolic Blood Pressure Intervention Trial.

Table S3: Key assumptions regarding alternate antihypertensive medication adherence scenarios

#	Scenario	First 5 years (planned SPRINT follow up)			After the first 5 years (model projection of SPRINT results)		
		Adherence Classification	**Assumption**	**Probability adherent**	**Adherence Classification**	**Assumption**	**Probability adherent**
1.	***Base-case***	Adherent vs. Non-adherent	All patients adherent to therapy	1.0	Adherent vs. Non-adherent	• 5-15 years: Intermittent adherence based on number of anti-HTN meds • After 15 years: All patients permanently non-adherent	• 5-15 years: ○ 1 med: 0.91[6] ○ 2 meds: 0.87[6] ○ ≥3 med: 0.83[6] • After 15 years: 0.0
2.	***Worst-case***		Same as base-case		Adherent vs. Non-adherent	• All patients permanently non-adherent at 5 years	• 0.0
3.	***Best-case until 15 years***		Same as base-case		Adherent vs. Non-adherent	• All patients adherent for first 15 years • All patients permanently non-adherent after first 15 years	• 5-15 years: 1.0 • After 15 years: 0.0
4.	***Best-case***		Same as base-case		Adherent vs. Non-adherent	• All patients permanently adherent to intensive treatment over their lifetime	• After 5 years: 1.0 each cycle
5.	***In-trial non-adherence***	Adherent vs. Non-adherent	Adherence based on number of anti-HTN meds	Probability intermittently adherent[6] ○ 1 med: 0.91 ○ 2 meds: 0.87	Same as base-case		

#	Scenario	First 5 years (planned SPRINT follow up)			After the first 5 years (model projection of SPRINT results)		
		Adherence Classification	**Assumption**	**Probability adherent**	**Adherence Classification**	**Assumption**	**Probability adherent**
				○ ≥3 med: 0.83[6]			
6.	***In trial discontinuation and non-adherence***	Adherent vs. Non-adherent	Patients were at risk of permanent discontinuation during 1st year of treatment If patients did not discontinue, patients were at risk of intermittent non-adherence	Probability permanently discontinue in 1st year: 0.25[35] Probability intermittently adherent • 1 med: 0.91[6] • 2 meds: 0.87[6] • ≥3 med: 0.83[6]	Same as base-case		
7.	***Alternate adherence estimates (post-trial only)***	Same as base-case			Adherent vs. Non-adherent	• 5-15 years: Intermittent non-adherence based on number of anti-HTN meds • After 15 years: All patients non-adherent	• 5-15 years: ○ 1 med: 0.79[36] ○ 2 meds:0.69[36] ○ 3 meds:0.65[36] ○ 4 meds:0.51[36] • After 15 years: 0.0 each cycle

#	Scenario	First 5 years (planned SPRINT follow up)			After the first 5 years (model projection of SPRINT results)		
		Adherence Classification	Assumption	Probability adherent	Adherence Classification	Assumption	Probability adherent
8.	***Permanent discontinuation post-trial period only***		Same as base-case		Adherent vs. Non-adherent	• 5-15 years: Intermittent non-adherence based on number of anti-HTN meds • After 15 years: All patients non-adherent	• 5-15 years: ○ 1 med: 0.91[6] ○ 2 meds: 0.87[6] ○ ≥3 med: 0.83[6] ○ After 1st time non-adherent: 0.0 • After 15 years: 0.0
9.	***Moderate post-trial medication adherence.***		Same as base-case		Non-adherent, Moderately adherent, or Adherent	• 5-15 years: Intermittent adherence based on number of anti-HTN meds • After 15 years: All patients permanently non-adherent • Based on Will et al.,[37] individuals could be intermittently moderately adherent or non-adherent • Based on Will et al.,[37] CVD event risk modified for moderately adherent compared to non-adherent	Adherent ○ 1 med: 0.91[6] ○ 2 meds: 0.87[6] ○ ≥3 med: 0.83[6] If less than adherent, probability moderately adherent: 0.63[6]

#	Scenario	First 5 years (planned SPRINT follow up)			After the first 5 years (model projection of SPRINT results)		
		Adherence Classification	**Assumption**	**Probability adherent**	**Adherence Classification**	**Assumption**	**Probability adherent**
						patients (HR: 0.93, 95%CI 0.92-0.94)	
10	***SPRINT Observed Adherence Estimates***	Adherent vs. Non-adherent	Self-reported adherence measured by Morisky scale Event risks as observed in SPRINT Direct Medical Costs tied to adherence	Probability intermittently adherent ○ 1 med: 0.82 ○ 2 meds: 0.86 ○ 3 meds: 0.86 ○ 4 meds: 0.83 ○ 5 meds: 0.81	Adherent vs. Non-adherent	Intermittent adherence based on number of anti-HTN meds Direct medical costs and events tied to adherence	○ 1 med: 0.82 ○ 2 meds: 0.86 ○ 3 meds: 0.86 ○ 4 meds: 0.83 ○ 5 meds: 0.81

Anti-HTN – antihypertensive, CI – Confidence interval, CVD – Cardiovascular disease, HR – Hazard ratio, SPRINT – Systolic Blood Pressure Intervention Trial.

Table S4: Diagnosis and procedure codes used to identify event costs

Event type	ICD-9 Code or CPT/HCPCS Code
CVD Event	*AHRQ HCUP*[17]
UA	411.1, 413.X
MI	410.X0, 410.X1
HF	428.XX
Stroke	430, 431, 432.X, 433.X , 434.X, 435.X, 436, 437.X
Sudden cardiac arrest	427.5
SAEs	*AHRQ HCUP*[17]
Hypotension	458.0, 458.29, 458.8, 458.9
Syncope	780.2
Bradycardia	427.81, 427.89
Electrolyte abnormality	791.9, 276
AKI	584, 586
Monitoring costs	*CMS physician or laboratory fee schedule*[12,13]
Hypertension management office visit	99214
Electrolyte monitoring	80048

AHRQ – Agency for Healthcare Research and Quality, AKI – acute kidney injury, CMS – Centers for Medicare and Medicaid Services, CPT – current procedural terminology, CVD – cardiovascular disease, HCPCS – healthcare common procedure coding system, HCUP – healthcare cost

and utilization project, HF- heart failure, ICD-9 – International Classification of Diseases 9th revision, MI – myocardial infarction, SAE – serious adverse event, UA – unstable angina.

Table S5: Assumptions for alternate scenario analyses not related to medication adherence

#	Scenario	Base-case assumption	Alternate scenario
Generalizability			
11	SPRINT-eligible general U.S. population (based on the U.S. National Health and Nutrition Examination Survey [NHANES]).	• Model populated using the characteristics of the SPRINT trial cohort.	• Model populated using the characteristics of the population sampled by the NHANES 2007-2012 and meeting the SPRINT-eligibility criteria (from Bress et al.[38])
Alternate Utility Sources			
12	HTN utility + median utilities	• No disutility for HTN • Mean utility values used for other comorbidities	• Median utilities used, including median utility for HTN • Based on Sullivan et al.[21]
13	Median utilities	• Mean utility values used for other comorbidities	• Median utility values used for other comorbidities, but utility for HTN excluded • Based on Sullivan et al.[21]
14	Health related quality of life for patients with hypertension, but no CVD diagnosis utility observed in SPRINT.	• Health state-specific utility estimates derived from Sullivan et al. but with utility of hypertension, but no CVD equal to 1.0 (asymptomatic/no disability).[21]	Utility estimates for hypertension but no CVD derived from mean EQ-5D estimates derived from SPRINT.
15	Alternate Utility Estimates	• Utility estimates derived from Sullivan et al.[21]	Utility estimates derived from other literature sources.[39-41]
16	Alternate No prior CVD (i.e., hypertension) Utility	• Utility estimates derived from Sullivan et al. and utility of no CVD (i.e., hypertension alone) was assumed to be 1.000.[21]	Multiple regression adjusted utility estimate of no CVD (i.e., hypertension alone) was 0.975.[21]
Pill-taking disutility			

#	Scenario	Base-case assumption	Alternate scenario
17	Increased pill-taking disutility with increased number of medications prescribed.	• No disutility for taking medications was included.	Additive per medication utility penalty of 0.002 based on the method reported by Hutchins et al.[42]
Assessing the impact of minor adverse events			
18	Minor medication-related adverse events	• Minor adverse events were not included.	• Added the risk of and disutility for experiencing symptoms due to minor adverse events.[43,44] No costs to the payer were assumed to incur for minor adverse events.
Antihypertensive medication cost scenarios			
19	NADAC Drug Costs	• Drug costs were derived from Red Book.	Used drug costs based on the National Average Drug Acquisition Cost (NADAC).
Serious adverse event Threshold Analyses			
20	Threshold analysis of SAEs in the post-trial period	• For adherent patients, the risk of SAEs was the same as observed in SPRINT. For non-adherent patients, the risk was the same as the standard treatment arm in SPRINT.	• The risk of SAEs in the post-trial period was increased until intensive treatment arm was no longer cost-effective (i.e., the ICER was >$50,000/QALY gained).
21	Threshold analysis of intensive SAE risk	• For adherent patients, the risk of SAEs was the same as observed in SPRINT. For non-adherent patients, the risk was the same as the standard treatment arm in SPRINT.	• The HR for the risk of SAEs in the intensive SBP treatment arm was increased until the intensive treatment arm was no longer cost-effective (i.e., the ICER was >$50,000/QALY gained).

#	Scenario	Base-case assumption	Alternate scenario
Modifying CVD Risk Prediction Scenarios			
22	Decreased Pooled Cohort Equation Risk	• Unaltered Pooled Cohort Risk Equations used to estimate the risk of a CVD event in non-adherent patients.	• A pooled, weighted observed-to-predicted ratio of CVD events in high-risk patients was derived from large cohort studies performed in the US.[45] This was applied to the estimated Pooled Cohort Risk of CVD events resulting in an approximate 36% reduction of risk.
23	Framingham Recurrent Coronary Heart Disease Equation used to predict recurrent CVD events	• Pooled Cohort Risk Equations used to estimate the risk of recurrent CVD events.	• The Framingham Recurrent Coronary Heart Disease Equation[46] was used to predict the risk of recurrent coronary heart disease events (includes mostly hospitalized events consisting of myocardial infarction, coronary insufficiency, angina pectoris, and sudden and non-sudden coronary death in patients with a history of events).
Office and laboratory visit scenarios			
24 to 27	Number of office visits	• Intensive vs. standard treatment, visits per year: 4 vs. 3 office, 2 vs. 1 laboratory	• Intensive vs. standard treatment, visits per year: 24. 4 vs. 2 office, 2 vs. 1 laboratory 25. First 5 years – 4 vs. 2 office and 2 vs. 1 laboratory, both after 5 years – 2 office and 1 laboratory 26. First year – 4 vs. 2 office and 2 vs. 1 laboratory, both after first year – 2 office and 1 laboratory 27. Both first 5 years – 4 office and 2 laboratory, after 5 years when adherent – 4 vs. 2 office and 2 vs. 1 laboratory, after 5 years when non-adherent – 2 office and 1 laboratory
Other Scenario Analyses			
28	Pooled cohort equation for CVD risk throughout	• CVD risk based on SPRINT results during the first 5 years	• CVD risk based on Pooled cohort equation over entire model time horizon, including first 5 years[33]

#	Scenario	Base-case assumption	Alternate scenario
29	Standard goal treatment effects for everyone after 5 years regardless of adherence	• Patients persist on treatment goal after the first 5 years	• All patients return to standard goal after first 5 years
30	CDC non-CVD mortality throughout	• Non-CVD mortality is based on SPRINT results in first 5 years, followed by CDC life-tables[34]	• Non-CVD mortality is based on CDC life-tables over entire model time horizon, including first 5 years[34]
31	Alternate CDC non-CVD mortality	• CDC mortality excluding major cardiovascular disease deaths[34]	• CDC mortality excluding hypertensive heart diseases[34]
32	Approximation of Richman et al.[47]	• See base-case description in Table S2	• HTN utility included, alternate non-CVD costs, and lifetime in-trial adherence and treatment effects
33	Alternate mortality after non-fatal CVD event using Peeters et al (base-case).[48]	• CDC non-CVD mortality was the same for those with and without cardiovascular disease	• Non-CVD mortality specific to those with and without CVD from Peeters et al for the base-case.[48]
34	Alternate mortality after non-fatal CVD event using Peeters et al (worst-case).[48]	• CDC non-CVD mortality was the same for those with and without cardiovascular disease	• Non-CVD mortality specific to those with and without CVD from Peeters et al for the worst-case.[48]
35	Alternate mortality after non-fatal CVD event using Peeters et al (best-case until 15 years).[48]	• CDC non-CVD mortality was the same for those with and without cardiovascular disease	• Non-CVD mortality specific to those with and without CVD from Peeters et al for the best-case until 15 years.[48]
36	Alternate mortality after non-fatal CVD event using Peeters et al (best-case).[48]	• CDC non-CVD mortality was the same for those with and without cardiovascular disease	• Non-CVD mortality specific to those with and without CVD from Peeters et al for the best-case.[48]

CDC – Centers for Disease Control and Prevention, CVD – cardiovascular disease, EQ-5D – EuroQol five-dimensions questionnaire, HR – Hazard ratio, HTN – hypertension, ICER – Incremental cost-effectiveness ratio, QALY – Quality-adjusted life-year, SAE – Serious adverse event, SBP – systolic blood pressure, SPRINT – Systolic Blood Pressure Intervention Trial.

Table S6: Comparison of simulation outputs to published SPRINT results at median SPRINT follow up of 3.3 years

	Intensive (<120 mmHg) Incidence rate (per 1000 person-years)			Standard (<140 mmHg) Incidence rate (per 1000 person-years)			Intensive vs. Standard Hazard Ratio (95%CI)	
	Model	**SPRINT**	**Abs. Diff.**	**Model**	**SPRINT**	**Abs. Diff.**	**Model**	**SPRINT**
Primary validation								
First CVD event or CVD death	17.3	16.5	0.8	22.2	21.9	0.3	0.78 (0.70-0.87)	0.75 (0.64-0.89)
Secondary validation								
CVD events								
Myocardial infarction	5.7	6.5	0.8	6.4	7.8	1.4	0.88 (0.72-1.08)	0.83 (0.64-1.09)
ACS/UA	2.1	2.7	0.6	2.2	2.7	0.5	0.99 (0.71-1.39)	1.00 (0.64-1.55)
Stroke	3.1	4.1	1.0	3.7	4.7	1.0	0.85 (0.65-1.11)	0.89 (0.63-1.25)
Heart failure	3.4	4.1	0.7	5.1	6.7	1.6	0.66 (0.51-0.83)	0.62 (0.45-0.84)
CVD death	3.0	2.5	0.5	4.8	4.3	0.5	0.62 (0.48-0.80)	0.57 (0.38-0.85)
All-cause mortality	11.0	10.3	0.7	14.4	14.0	0.7	0.77 (0.67-0.88)	0.73 (0.60-0.90)
Non-CVD mortality	7.5	7.8	0.3	9.3	9.6	0.3	0.81 (0.68-0.96)	0.81 (0.64-1.03)
SAEs of interest (i.e., only those included in the model)								

Hypotension	9.6	10.6	1.0	4.7	6.2	1.5	2.04 (1.68-2.48)	1.70 (1.24-2.33)
Syncope	9.8	10.9	1.1	6.2	7.5	0.7	1.59 (1.33-1.90)	1.44 (1.13-1.83)
Bradycardia	6.5	6.8	0.3	5.0	5.6	0.6	1.32 (1.07-1.62)	1.25 (0.94-1.67)
Electrolyte abnormality	11.2	11.9	0.7	7.5	8.7	1.2	1.49 (1.27-1.75)	1.38 (1.10-1.73)
AKI	13.0	13.8	0.8	7.1	8.1	1.0	1.83 (1.56-2.15)	1.71 (1.24-2.35)

Abs. Diff – Absolute difference, ACS/UA – Acute coronary syndrome/unstable angina, AKI – Acute kidney disease, CI – Confidence interval, CVD – Cardiovascular disease, HF – Heart failure, mmHg – Millimeters of mercury, SAEs – Serious adverse events, SPRINT – Systolic Blood Pressure Intervention Trial.

Table S7: Lifetime simulated cardiovascular disease events across the four different post-trial period adherence and treatment effect scenarios

	Mean Remaining Life Expectancy	Primary Outcome		CVD Death		All CVD Events or CVD Death	
		Cumulative incidence	*Incidence Rate (Per 1000 Person-years)*	*Cumulative incidence*	*Incidence Rate (Per 1000 Person-years)*	*Cumulative incidence*	*Incidence Rate (Per 1000 Person-years)*
Base-case							
Intensive	18.99	41.69%	27.67	10.79%	5.68	59.92%	31.49
Standard	18.53	43.39%	29.84	12.69%	6.85	62.04%	33.49
Worst-case							
Intensive	18.86	46.46%	32.02	11.91%	6.31	67.89%	35.99
Standard	18.47	47.05%	33.23	13.65%	7.39	68.40%	37.02
Best-case until 15 years							
Intensive	19.19	37.68%	24.16	9.30%	4.85	51.94%	27.07
Standard	18.65	41.66%	28.28	11.80%	6.33	57.67%	30.92
Best-case							
Intensive	19.57	31.27%	19.09	5.93%	3.03	38.01%	19.42
Standard	19.03	40.56%	26.56	10.57%	5.56	52.53%	27.61

The four different post-trial adherence and treatment effect scenarios are shown: base-case (i.e., decay in adherence and treatment effects after five years until non-adherent and no treatment effects at 15 years), non-adherence and no treatment effects after five years, in-trial adherence and treatment effects persists for 15 years, and lifetime in-trial adherence and treatment effects.

CVD – cardiovascular disease

Table S8: Direct medical costs (2017 USD), reported by type, from probabilistic analyses

	Mean Intensive	Mean Standard	Incremental	95% Uncertainty Interval	
				Lower Limit	Upper Limit
Base-case					
Total	$284,637	$271,841	$12,796	-$872	$26,551
CVD Event	$5,414	$5,728	-$314	-$2,749	$2,024
SAE	$5,319	$3,596	$1,723	-$437	$4,484
Non-CVD Medical Costs	$208,803	$201,702	$7,102	$2,248	$14,060
Chronic CVD	$52,395	$52,432	-$37	-$13,326	$13,937
Treatment*	$12,704	$8,382	$4,322	$2,799	$5,851
Worst-case					
Total	$283,401	$270,965	$12,436	-$2,148	$28,091
CVD Event	$6,184	$6,317	-$133	-$2,915	$2,771
SAE	$4,615	$3,603	$1,012	-$1,052	$3,327
Non-CVD Medical Costs	$207,358	$200,034	$7,325	$2,492	$14,169
Chronic CVD	$56,523	$54,920	$1,603	-$12,767	$17,746
Treatment*	$8,720	$6,091	$2,629	$2,024	$3,285
Best-case until 15 years					
Total	$286,161	$274,163	$11,998	-$862	$25,365
CVD Event	$4,685	$5,313	-$628	-$2,722	$1,305
SAE	$5,826	$3,497	$2,329	$156	$5,470
Non-CVD Medical Costs	$210,441	$203,233	$7,208	$2,194	$14,484
Chronic CVD	$49,435	$51,148	-$1,713	-$14,574	$10,869
Treatment*	$15,774	$10,972	$4,802	$3,076	$6,519
Best-case					

	Mean Intensive	Mean Standard	Incremental	95% Uncertainty Interval	
				Lower Limit	Upper Limit
Total	$285,909	$274,146	$11,763	-$5,386	$29,232
CVD Event	$3,776	$5,074	-$1,297	-$4,620	$1,641
SAE	$5,418	$3,394	$2,025	-$135	$4,752
Non-CVD Medical Costs	$214,631	$204,392	$10,239	$4,440	$17,879
Chronic CVD	$46,390	$50,551	-$4,161	-$20,879	$11,641
Treatment*	$15,693	$10,736	$4,957	$3,246	$6,732

*Treatment costs included antihypertensive medications, office visits, and laboratory visits

CVD – Cardiovascular disease, SAE – Serious adverse event, USD – United States dollars

Table S9: Direct medical costs, effectiveness, and incremental cost-effectiveness results of probabilistic analyses in subgroups

	Mean Total Costs (2017 USD)	Incremental Costs (95% UI)	Mean Remaining Lifetime QALYs	Incremental QALYs (95% UI)	ICER (Cost/QALY gained)	Probability Cost-effective		
						$50k/QALY	$100k/QALY	$150k/QALY
Previous CKD								
Intensive	$325,224	$11,462	12.03	0.30	$38,601	62%	81%	86%
Standard	$313,763	(-$4,884, $30,831)	11.73	(-0.11, 0.75)	-	-	-	-
No Previous CKD								
Intensive	$270,435	$13,895	12.59	0.25	$56,420	45%	75%	83%
Standard	$256,540	($489, $27,944)	12.35	(-0.07, 0.56)	-	-	-	-
Age <75								
Intensive	$292,063	$13,720	13.74	0.27	$50,000	51%	78%	86%
Standard	$278,343	(-$475, $29,037)	13.46	(-0.07, 0.63)	-	-	-	-
Age ≥75								
Intensive	$266,155	$7,656	9.11	0.30	$25,697	79%	93%	96%
Standard	$258,498	(-$4,687, $19,627)	8.81	(0.02, 0.60)	-	-	-	-
Female								
Intensive	$327,854	$14,189	13.06	0.19	$76,606	32%	60%	70%
Standard	$313,664	($1,532, $28,677)	12.87	(-0.17, 0.55)	-	-	-	-
Male								
Intensive	$260,596	$11,756	12.11	0.29	$40,199	61%	83%	89%
Standard	$248,841	(-$1,840, $26,907)	11.81	(-0.04, 0.65)	-	-	-	-

	Mean Total Costs (2017 USD)	Incremental Costs (95% UI)	Mean Remaining Lifetime QALYs	Incremental QALYs (95% UI)	ICER (Cost/QALY gained)	Probability Cost-effective		
						$50k/QALY	$100k/QALY	$150k/QALY
Black								
Intensive	$282,555	$12,262	12.65	0.22	$55,287	46%	71%	79%
Standard	$270,294	($436, $25,750)	12.43	(-0.11, 0.58)	-	-	-	-
Non-Black								
Intensive	$285,792	$13,502	12.36	0.30	$44,493	57%	84%	89%
Standard	$272,291	(-$242, $29,049)	12.06	(-0.05, 0.64)	-	-	-	-
Previous CVD								
Intensive	$393,274	$17,160	9.38	0.24	$71,740	41%	60%	70%
Standard	$376,114	(-$15,939, $55,881)	9.14	(-0.16, 0.72)	-	-	-	-
No Previous CVD								
intensive	$282,740	$12,490	12.56	0.25	$49,691	51%	79%	86%
Standard	$270,250	($501, $26,166)	12.31	(-0.03, 0.54)	-	-	-	-

CKD – Chronic kidney disease, CVD – Cardiovascular disease, ICER – Incremental cost-effectiveness ratio, QALYs – Quality-adjusted life-years, UI – Uncertainty interval, USD – United States dollars.

Table S10. Non-probabilistic analyses of costs, effectiveness, and incremental cost-effectiveness results in scenario analyses

#	Scenario	Mean Costs (2017 USD)	Mean QALYs	ICER (Cost/ QALY gained)
Main Scenarios				
1	Base-case			
	Intensive	$288,926	12.34	$44,272
	Standard	$275,595	12.04	-
2	Worst-case			
	Intensive	$287,799	12.19	$45,619
	Standard	$276,757	11.95	-
3	Best-case until 15 years			
	Intensive	$289,320	12.52	$33,731
	Standard	$276,682	12.14	-
4	Best-case			
	Intensive	$286,904	12.75	$24,143
	Standard	$277,022	12.34	-
Medication Adherence Scenarios				
5	In-trial non-adherence			
	Intensive	$287,008	12.25	$49,622
	Standard	$274,079	11.98	-
6	In trial discontinuation and non-adherence			
	Intensive	$286,334	12.24	$46,621
	Standard	$274,464	11.98	-
7	Alternate adherence estimates (post-trial only)			

#	Scenario	Mean Costs (2017 USD)	Mean QALYs	ICER (Cost/ QALY gained)
	Intensive	$288,986	12.29	$44,738
	Standard	$276,438	12.01	-
8	Permanent discontinuation post-trial period only			
	Intensive	$285,956	12.33	$38,178
	Standard	$273,968	12.01	-
9	Moderate post-trial medication adherence			
	Intensive	$288,328	12.36	$44,462
	Standard	$275,010	12.06	-
10	SPRINT observed adherence estimates			
	Intensive	$288,873	12.35	$42,281
	Standard	$276,020	12.04	-
Generalizability				
11	SPRINT-eligible general U.S. population (based on NHANES)			
	Intensive	$281,198	12.32	$46,113
	Standard	$266,960	12.01	-
Alternate Utility Sources				
12	HTN utility + median utilities			
	Intensive	$288,926	10.98	$52,800
	Standard	$275,595	10.72	-
13	Median utilities			
	Intensive	$288,926	12.69	$43,946
	Standard	$275,595	12.38	-
14	Health related quality of life for patients with hypertension, but no CVD diagnosis, using utility observed in SPRINT with EQ-5D			
	Intensive	$288,926	10.81	$52,176

#	Scenario	Mean Costs (2017 USD)	Mean QALYs	ICER (Cost/ QALY gained)
	Standard	$275,595	10.55	-
15	Alternate utility estimates			
	Intensive	$288,926	12.50	$41,666
	Standard	$275,595	12.18	-
16	Alternate no prior CVD (i.e., hypertension) utility			
	Intensive	$288,926	12.11	$45,312
	Standard	$275,595	11.81	-
Pill-taking disutility				
17	Increased pill-taking disutility with increased number of medications prescribed			
	Intensive	$288,926	12.24	$49,308
	Standard	$275,595	11.97	-
Assessing the impact of minor adverse events				
18	Minor adverse events			
	Intensive	$288,926	12.32	$44,744
	Standard	$275,595	12.02	-
Antihypertensive medication cost scenarios				
19	NADAC drug costs			
	Intensive	$285,999	12.34	$40,162
	Standard	$273,906	12.04	-
Serious adverse event threshold analyses				
20	Threshold analysis of SAEs in the post-trial period		Results presented in Figure S12	
21	Threshold analysis of intensive SAE risk		Results Presented in Figure S13	
Modifying CVD Risk Prediction Scenarios				
22	Decreased Pooled Cohort risk equations			
	Intensive	$284,184	12.59	$37,919
	Standard	$272,438	12.28	-
23	Framingham Recurrent Coronary Heart Disease Equation used to predict recurrent CVD events			

#	Scenario	Mean Costs (2017 USD)	Mean QALYs	ICER (Cost/ QALY gained)
	Intensive	$289,626	12.36	$43,970
	Standard	$275,520	12.04	-
Number of office and laboratory visit scenarios (Intensive vs. standard treatment, visits per year)				
24	4 vs. 2 office, 2 vs. 1 laboratory			
	Intensive	$288,926	12.34	$49,158
	Standard	$274,123	12.04	-
25	First year – 4 vs. 2 office and 2 vs. 1 laboratory, both after first year – 2 office and 1 laboratory			
	Intensive	$286,755	12.34	$41,951
	Standard	$274,123	12.04	-
26	First 5 years – 4 vs. 2 office and 2 vs. 1 laboratory, both after 5 years – 2 office and 1 laboratory			
	Intensive	$285,924	12.34	$39,191
	Standard	$274,123	12.04	-
27	Both first 5 years – 4 office and 2 laboratory, after 5 years when adherent – 4 vs. 2 office and 2 vs. 1 laboratory, after 5 years when non-adherent – 2 office and 1 laboratory			
	Intensive	$287,977	12.34	$42,510
	Standard	$275,177	12.04	-
Other Scenario Analyses				
28	Pooled cohort equation for CVD risk throughout			
	Intensive	$291,351	12.25	$75,956
	Standard	$277,704	12.07	-
29	Standard goal treatment effects for everyone after 5 years regardless of adherence			
	Intensive	$286,719	12.38	$49,916
	Standard	$274,517	12.13	-
30	CDC non-CVD mortality throughout			
	Intensive	$274,842	11.86	$51,610
	Standard	$264,408	11.66	-
31	Alternate CDC non-CVD mortality			
	Intensive	$228,773	10.91	$39,959

#	Scenario	Mean Costs (2017 USD)	Mean QALYs	ICER (Cost/ QALY gained)
	Standard	$219,353	10.68	-
32	Approximation of Richman et al.[47]			
	Intensive	$244,709	10.64	$37,121
	Standard	$233,037	10.32	-
33	Alternate mortality after non-fatal CVD event using Peeters et al (base-case).[48]			
	Intensive	$272,145	12.11	$44,561
	Standard	$258,937	11.82	-
34	Alternate mortality after non-fatal CVD event using Peeters et al (worst-case).[48]			
	Intensive	$268,686	11.94	$44,088
	Standard	$258,522	11.71	-
35	Alternate mortality after non-fatal CVD event using Peeters et al (best-case until 15 years).[48]			
	Intensive	$274,971	12.32	$35,818
	Standard	$261,445	11.94	-
36	Alternate mortality after non-fatal CVD event using Peeters et al (best-case).[48]			
	Intensive	$276,308	12.57	$27,321
	Standard	$264,195	12.12	

Scenarios 20 and 21, the SAE threshold analyses, are presented in Figure S12 and S13 and on page 24 and 25 of text.

CDC – Centers for Disease Control and Prevention, CKD – Chronic kidney disease, CVD – Cardiovascular disease, HTN – Hypertension, ICER – Incremental cost-effectiveness ratio, NADAC – National Average Drug Acquisition Cost, NHANES – U.S. National Health and Nutrition Examination Survey, QALY – quality-adjusted life-year, SAE – Serious adverse event, SPRINT – Systolic Blood Pressure Intervention Trial, USD – United States dollars

Table S11: Adherence to CHEERS CEA checklist.[49]

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page #/line #
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Title page (Page 1)
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Pages 2 & 3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Pages 4
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Pages 5 & 6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Pages 5 & 6

Section/item	Item No	Recommendation	Reported on page #/line #
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 7
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Pages 5-8 & Table 1
Measurement of effectiveness	11a	*Single study-based estimates*: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	Not applicable
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Page 8 & Table 1
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Not applicable
Estimating resources and costs	13a	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not applicable
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Pages 5-8 & Table 1 (Note: indirect and opportunity costs not considered)
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 7-8 & Table 1
Choice of model	15	Describe and give reasons for the specific type of decision- analytical model used. Providing a figure to show model structure is strongly recommended.	Page 5 & Figure 1

Section/item	Item No	Recommendation	Reported on page #/line #
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Pages 5-7, Figure 1, & Supplement Pages 4-12 & Tables S2-S4
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Pages 5-9 & Supplement pages 4-12
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1 & Table S1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Tables 1 & 2, Figure 2 & 3
Characterising uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Not applicable
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Pages 10-12, Table 2, Figure 2 & 3, & Tables S7, S8, S10 & Figures S5, S6, S9-S13
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost- effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Table S9
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Pages 12-16

Section/item	Item No	Recommendation	Reported on page #/line #
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 17 - 18
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 18

Table S12: Reporting checklist for cost-effectiveness analyses from the Second Panel on Cost-effectiveness in Health and Medicine[50]

Element	Journal Article	Technical Supplement
Introduction		
Background of the problem	Pages 4	
Study Design and Scope		
Objectives	Page 5	
Audience		
Type of analysis	Page 5	Supplement Page 4
Target populations	Page 5	Supplement Page 4
Description of interventions and comparators (including no intervention, if applicable)	Page 5	Supplement Page 4
Other intervention descriptors (e.g., care setting, model of delivery, intensity and timing of intervention)	Figure 1 footnote	Supplement Page 4
Boundaries of the analysis; defining the scope or comprehensiveness of the study (e.g., for a screening program, whether only a subset of many possible strategies are included; for a transmissible condition, the extent to which disease transmission is captured; for interventions with many possible delivery settings, whether only one or more settings are modeled)	Pages 4 & 5	
Time horizon	Page 5	
Analytic perspectives (e.g., reference case perspectives [health care sector, societal]; other perspectives such as employer or payer)	Page 5	
Whether this analysis meets the requirements of the reference case	Page 8	
Analysis plan		Supplement Pages 4-12
Methods and Data		
Trial-based analysis or model-based analysis. If model-based:		
Description of event pathway or model (describe condition or disease and the health states included)	Pages 5-7 & Figure 1	Supplement Pages 4-9
Diagram of event pathway or model (depicting the sequencing and possible transitions among the health states included)	Figure 1	Figure S1-S2
Description of model used (e.g., decision tree, state transition, microsimulation)	Page 5	Supplement Page 4-9

Element	Journal Article	Technical Supplement
Modeling assumptions	Pages 5-7 & Figure 1-3	Supplement Pages 4-12 & Tables S2-S4
Software used		Supplement Page 5
Identification of key outcomes	Pages 5-8	Supplement Pages 4-10
Complete information on sources of effectiveness data, cost data, and preference weights	Table 1	Supplement Table S1
Methods for obtaining estimates of effectiveness (including approaches used for evidence synthesis)	Pages 5-8	Supplement Pages 8-10 & Table S1
Methods for obtaining estimates of costs and preference weights	Pages 7-8	Supplement Pages 8-10 & Table S1
Critique of data quality		
Statement of costing year (i.e., the year to which all costs have been adjusted for the analysis; e.g., 2017)	Page 7	
Statement of method used to adjust costs for inflation	Page 7	
Statement of type of currency	Page 7	
Source and methods for obtaining expert judgment if applicable		
Statement of discount rates	Page 7	
Impact Inventory		
Full accounting of consequences within and outside the health care sector	Page 8	Supplement Pages 9-10
Results		
Results of model validation	Page 9-10	Figure S3-S6 & Table S6
Reference case results (discounted and undiscounted): total costs and effectiveness, incremental costs and effectiveness, incremental cost-effectiveness ratios, measures of uncertainty	Pages 10 &11 & Table 2	
Disaggregated results for important categories of costs, outcomes, or both	Table 2	Tables S8
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Other estimates of uncertainty	Page 12	
Graphical representation of cost-effectiveness results	Figure 3	Figures S10

Element	Journal Article	Technical Supplement
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Disclosures		
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Discussion of the study results in the context of results of related cost-effective analyses	Page 13	
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Limitations of the study	Page 15	
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