Supplementary Online Content

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

eAppendix. Methods

1. Parameter derivation:

a. Mortality:

We used data from CDC Life Tables to estimate mortality at each one-year age interval for those who were hypertensive and at risk of complications. CDC Life Tables report the number of individual surviving at each year of age.[1] CDC Life Tables also report the proportion of deaths attributable to cardiovascular disease at 5 year intervals.[2] We inflated the proportion of death attributable to CVD at age 75 (the approximate median age among those who died in SPRINT) to match that reported in the control arm of SPRINT. We also increased the proportion of death attributable to CVD at other ages by the same factor. This approach preserved the relative proportion of death attributable to CVD across ages. Using this approach, we calculated the yearly probability of death from cardiovascular and noncardiovascular causes at each age. Yearly probabilities were converted to monthly probabilities assuming an exponential distribution with a constant rate of death over each 12-month interval.

For those in the intensive treatment arm, we reduced the cardiovascular death rate by an average hazard ratio of 0.57 and noncardiovascular death by 0.77, the hazard ratios described in SPRINT. The cycle-specific hazard ratios we used were varied within the first 3 years for improved calibration but averaged to values reported in SPRINT over the duration of the model and in the first 3.26 years, the median follow up time of the trial.

Once participants developed cardiovascular disease, we calculated age- and disease-specific mortality using the following approach. First, we identified population-based estimates of all-cause mortality among survivors of MI and stroke and among those with heart failure.[3–6] Using these studies, we calculated monthly mortality rates assuming an exponential distribution. Then, we calculated age-specific mortality rates from CDC Life Tables at the mean ages reported in each of those studies. We subtracted this age-specific rate from rates reported in these observational studies to obtain the component of mortality (i.e., excess mortality) attributable to that disease. We then added that disease-specific mortality component to overall mortality at every age from 68 to death in our model. This approach assumes that the disease-specific component of mortality does not change with age.

b. Adverse Events:

Serious adverse events: We included a generic “serious adverse event” in our model. This simplified form allowed for more flexibility in sensitivity analysis. SPRINT reported that four serious adverse events were more common in the intensive blood pressure management arm: syncope, hypotension, electrolyte abnormalities, and acute kidney injury. We used the sum of the probabilities of these events as the basis of the probability of a generic serious adverse event in our model. The hazard ratio for major adverse events in our model was also based on these rates. We assumed that costs and disutilities for other adverse events that did not differ between treatment arms (but that were reported in SPRINT) were incorporated into the general

costs and disutility of hypertension. Our approach assumed that experiencing a serious adverse event did not lead to drug discontinuation.

Minor adverse events and medication side effects were not reported in the main analysis from SPRINT so we used rates from the published literature to inform our model. We used population-based estimates of the prevalence of adverse events and side effects among people taking two versus three antihypertensive medications to inform our model.[7] The relative risk of side effects for two versus three drugs was supported by findings from a meta analysis of hypertension treatment.[8]

c. Costs

We estimated costs associated with hypertension and cardiovascular disease primarily from two sources. First, we used age-specific average yearly Medicare expenditures as reported by Neuman et al. to delineate background costs for each year of age.[9] These costs include payments for all services billed under Medicare parts A, B, and D, but do not include expenditures paid by supplemental insurance, longterm care insurance, Medicaid, or out of pocket. These background costs take into account costs of common diseases accounted for elsewhere in our model, such as hypertension, MI, stroke, and heart failure. To address this, we estimated age-specific costs attributable to hypertension treatment, MI, heart failure, and stroke in the standard treatment arm of our model. We subtracted disease specific costs from average Medicare costs, assuming about 70% of the Medicare population has hypertension to get true baseline costs.

We estimated costs associated with cardiovascular disease based on work by Duh et al.[10] Duh et al. report quarterly costs for hypertensive adults before and after cardiovascular events. Using this, we estimated the incremental cost of an acute MI, stroke, or symptomatic heart failure. These costs include all inpatient and outpatient costs during the 3-month period following an event. We also used costs 6 months post event less pre-event costs to represent marginal chronic costs associated with cardiovascular disease.

We calculated costs of serious adverse events for syncope, hypotension, acute kidney injury, and electrolyte abnormalities, which were the adverse events reported to be significantly more common in the intensive blood pressure management arm of SPRINT. Serious adverse event costs reflect the costs of hospitalization for treatment of adverse events. To calculate these costs, we used the cost for a typical hospitalization for that indication as reported by the National Inpatient Sample/Healthcare Cost and Utilization Project (HCUP).[11] HCUP reports charge and estimates cost by applying a charge-to-cost ratio. We estimated physician fees based on a 4-day stay using the following CPT codes for admission, discharge, and subsequent evaluation: 99222, 99239, 99232.[12] Costs for these adverse events ranged between $6,227-$8,162. In our main model, for conceptual simplicity and for ease of manipulation in sensitivity analysis, we modeled a generic adverse event. We used a cost of $7,151 per adverse event,

which was the average of specific serious adverse event costs, weighted by the frequency reported in the standard arm in SPRINT.

We based costs of physician visits on Medicare reimbursement rates as described in the main text. We assumed that those in the intensive treatment arm saw their physicians about 3 times a year for the first 3 years and 2 times a year subsequently. Those in the standard treatment arm were seen twice yearly. This frequency is based is based on expert judgment and assumes that most patients will reach stability after several years of treatment even in the intensive treatment arm. Physician visits were somewhat less frequent in our model than in SPRINT, but we felt the visit frequency described in SPRINT may not be feasible in non-trial settings. Patients outside of a trial may also have medications titrated by nurses or pharmacists, over the phone, etc. Since we made a number of assumptions about physician visit frequency, we investigated costs of physician visits in a sensitivity analysis.

Drug costs were based on work done by Moran et al.[13] We used the mean of the upper and lower bound for 2 and 3 standard doses, inflated to 2016 prices.

d. Utilities

We used health state utilities estimated for a nationally representative population using the EQ-5D, as reported by Sullivan et al.[14] Sullivan et al. report both age-specific baseline utilities and marginal disutilities associated with specific chronic conditions (including hypertension, MI, stroke, and heart failure). We used these values, along with published data about age-specific prevalence of hypertension and cardiovascular disease, to calculate true baseline age-specific utilities (i.e. age-specific utilities that that did not incorporate a disutility for hypertension).[15] For example, let u equal the true underlying age-specific utility, not incorporating any effect of hypertension. Let m equal the measured utility at that age and h equal the marginal disutility from hypertension. P equals the proportion of the population with hypertension.

$m=p*(u-h)+(1-p)*(u).$

Solving for u gives the age-specific utility, not incorporating the effect of hypertension in that population. We then used these values as our baseline age-specific utilities from which we subtracted the disutility for hypertension. We repeated the same procedure for cardiovascular disease states, removing the disutilities for MI, stroke, and heart failure. For those steps, we used age-specific prevalences of those conditions.[5,15] We then added this new baseline utility to the marginal disease specific utilities reported in Sullivan et al. to obtain overall disease specific utilities. We assumed disutilities were additive.

Disutilities associated with serious adverse events were not readily available. We assumed, based on clinical judgment and previous published work, a disutility of -0.5 for one week associated with each serious adverse event.[13] We assumed that after an adverse event, the person returned to his or her previous state of health.

e. Treatment effects:

We used the point estimate of the hazard ratios for myocardial infarction, stroke, and heart failure as reported in SPRINT. Hazard ratios for cardiovascular and noncardiovascular death are described above. We did not explicitly model classes of medications, but assumed that treatment effects described in SPRINT reflected an average treatment effect produced by using a number of common medications in the study population.

2. Calibration:

We empirically calibrated our model to 3 targets. First, we ensured that all-cause mortality in our model matched all-cause mortality in each arm of SPRINT. We extracted data from the Kaplan-Meier cumulative mortality plots published with SPRINT using a visual data extraction tool.[16] Using this data, we plotted survival curves from SPRINT. We also used this data, along with the number of at-risk individuals reported for each year of trial follow up, to calculate the approximate 95% confidence intervals for these curves. In order to calibrate all-cause mortality in our model to fall within the 95% confidence interval from SPRINT, we reduced both cardiovascular and non-cardiovascular mortality by a factor of 0.45 in each arm. We also varied the hazard ratio for mortality from cycle to cycle within the first 39 months such that the average hazard ratio equal to what was reported in the trial.

We also calibrated event rates to SPRINT. We first calibrated event-free survival at 39 months in our model to what was reported in SPRINT at the mean follow up time. We then ensured that event rates (MI, heart failure, stroke) did not exceed rates reported in SPRINT, as rates reported in SPRINT were any event, including fatal events and second events.

When calibrating our model to mortality rates in NHANES, we used the following approach. We used data from Continuous NHANES 2001-2004, for which all-cause mortality data are available.[17] We identified participants who broadly met SPRINT inclusion criteria (hypertensive, age 50 or older, high risk for cardiovascular disease, as defined in SPRINT and SPRINT exclusion criteria (no history of stroke, no diabetes, no heart failure, no cancer diagnosis). We further selected this population to have a blood pressure range 110-180 with a mean of 136 to represent the standard treatment arm. Within this population, we plotted all-cause mortality and found that all-cause mortality in our model largely replicated all-cause mortality in this cohort (eFigure1).

For this analysis in which all-cause mortality is calibrated to the NHANES population, we used cardiovascular disease incidence rates from the Cardiovascular Health Study, which reports age-specific rates of nonfatal MI, heart failure, and nonfatal stroke.[18] In our main analysis, we had calibrated these rates to match rates reported in SPRINT. For this sensitivity analysis, we use uncalibrated rates, which are more representative of rates in the general population than in the SPRINT population specifically.

3. Deterministic Sensitivity Analyses:

We chose ranges for one-way sensitivity analyses based on plausible ranges for values including 95% confidence intervals, when available. When evaluating cost-effectiveness among the elderly, we used the mortality benefit as reported in SPRINT among adults >75 and adverse event rates among adults >75. SPRINT reported the hazard ratio for all-cause mortality among those >75 years. We assumed the reduction in non-cardiovascular death was similar to what was reported for the entire SPRINT population and that the proportion of noncardiovascular and cardiovascular death was also similar to what was reported in the trial overall. Using this information, we calculated the hazard ratio for CV mortality for those >75 years of age.

As in our main analysis, we modeled a generic category of serious adverse events based on the rates of hypotension, syncope, acute kidney injury, and electrolyte abnormalities. Though these serious adverse events were not all statistically significantly different in the intensive treatment arm among the elderly, we used them for consistency with our base case.

For our sensitivity analysis at age 50, we used cardiovascular disease event rates from the Framingham offspring study.[18] We calculated background healthcare costs as described previously, but used average yearly costs in the non-Medicare population.[19]

When evaluating how a reduced efficacy would alter our ICER, we reduced all benefits (cardiovascular mortality, noncardiovascular mortality, hazard ratio for MI, stroke, and heart failure) by 50%. This factor was based on an upper bound for estimates of nonadherence, although the relationship between nonadherence and health outcomes is less well characterized.[20,21]

4. Probabilistic Sensitivity Analysis

We performed a probabilistic sensitivity analysis (PSA) for our base case. We assigned uncertainty distributions for all parameters that had any uncertainty. We did not include data from CDC life tables in the PSA. We chose standard distributions to inform the PSA. For some model values, distribution parameters were not readily available. In those cases, we chose parameter values similar to others in the literature. These sources are noted in the eTable.

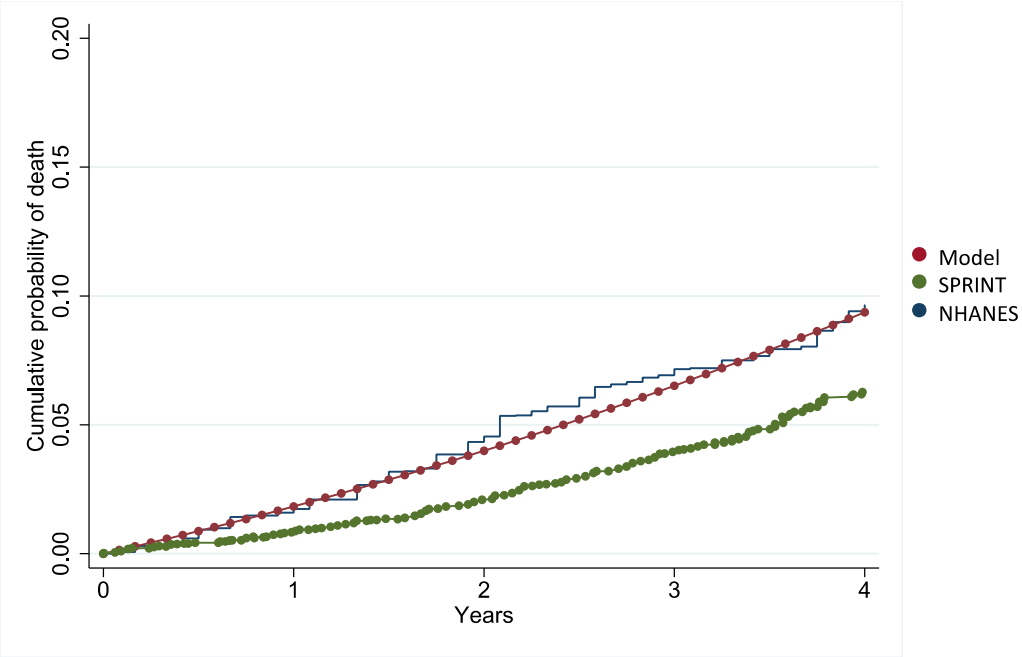
After assigning uncertainty distributions to model inputs, we randomly sampled from each distribution simultaneously. With 10,000 such samples, we reran the analysis to determine the proportion of samples in which intensive blood pressure management was the preferred strategy at a given willingness-to-pay threshold.

5. Software:

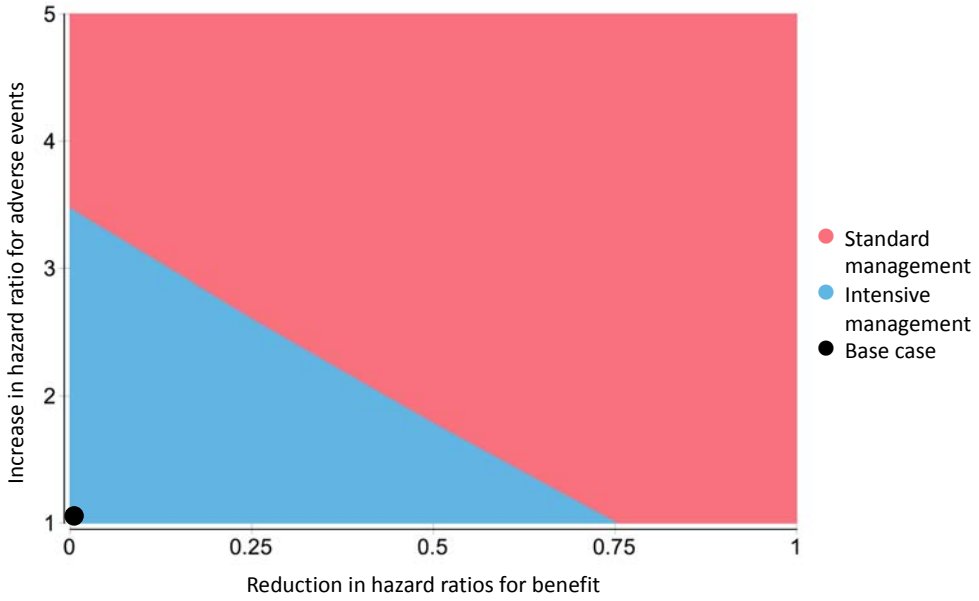
We performed the Markov modeling, sensitivity analyses, and probabilistic sensitivity analysis in TreeAge. We used Excel to process much of the data prior to entry into TreeAge (including life

tables, costs by year of age, and age-specific utilities). We used Stata to produce all of the survival curve and calibration figures.

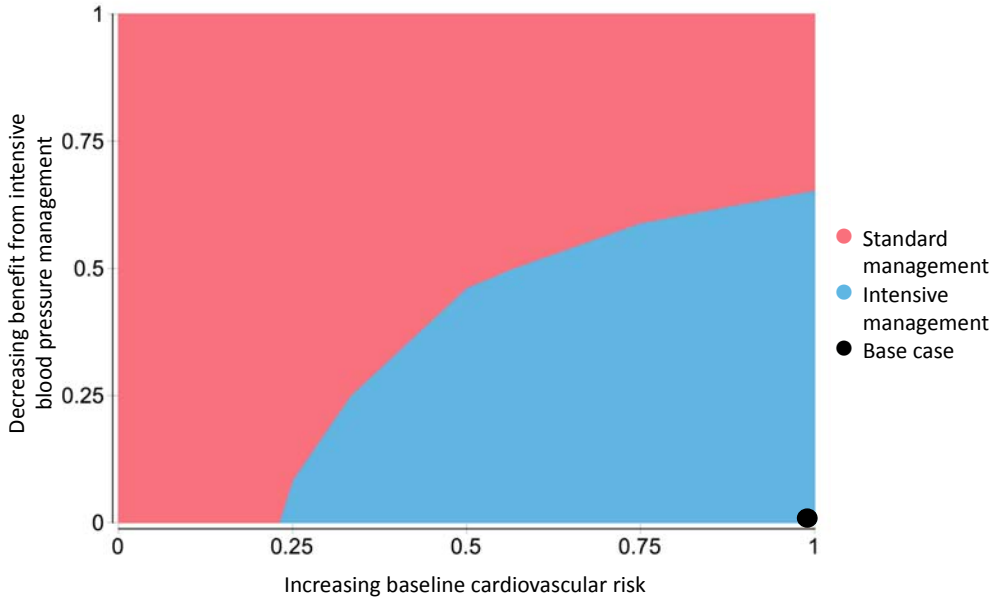
eFigure 1. Cumulative All-Cause Mortality in the SPRINT Standard Treatment Arm, the NHANES cohort, and the Model Standard Treatment Arm, Calibrated to the NHANES Cohort



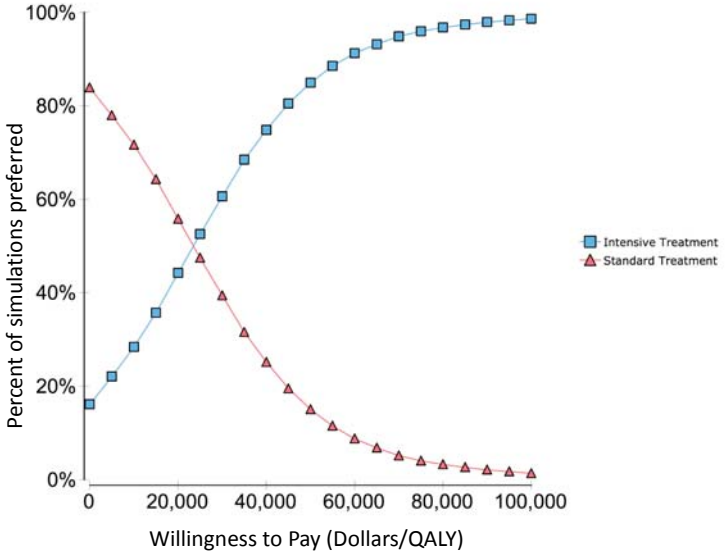
eFigure 2. Two-Way Sensitivity Analysis of Benefits and Harms. The X axis represents a decreasing benefit from 0 (benefits as described in SPRINT) to 1 (no benefit). The Y axis represents an increasing hazard ratio for adverse events from 1 (hazard ratio as described in SPRINT) to 5 (5 fold the hazard ratios). Figure assumes a willingness to pay threshold of $50,000.



eFigure 3. Two-Way Sensitivity Analysis of Baseline Cardiovascular Risk and Benefit of Intensive Blood Pressure Management. The X axis represents increasing risk of cardiovascular disease from no risk (lower left) to that reported in SPRINT (lower right). The Y axis represents decreasing benefits of intensive blood pressure management from 0 (benefits are as reported in SPRINT) to 1 (hazard ratio of 1).



eFigure 4. Cost-effectiveness Acceptability Curve. Figure shows the preferred strategy from probabilistic sensitivity analysis over a range of willingness-to-pay thresholds.



eTable. Distributions and Parameters for Probabilistic Sensitivity Analysis

Costs	Distribution	Mean	Standard Deviation	Notes and Sources
Background cost at age 68	gamma	543	961	For costs, SD is 177% of the mean, from Medicare estimates. 9, 22
Incremental monthly cost post MI	gamma	612	1,083	10
Incremental cost of acute MI	gamma	28,983	51,300	10
Incremental monthly cost post stroke	gamma	365	646	10
Incremental cost of acute stroke	gamma	6,909	12,229	10
Incremental monthly cost post HF	gamma	674	1,193	10
Incremental cost of acute HF	gamma	8,671	1041	10
Cost of physician visits (monthly, standard group)	gamma	14	25	12
Cost of hypertensive medication (2 medications)	gamma	38	67	13
Cost of serious adverse event	gamma	7,151	12,657	11,12
Cost of minor adverse event	gamma	1	1.77	Expert opinion
Benefits and Risks	**Distribution**	**Mu**	**Standard Deviation**	**Sources**
HR cardiovascular death	log normal	-0.562	0.205	23
HR noncardiovascular death	log normal	-0.315	0.145	23
HR MI	log normal	-0.186	0.200	23
HR Stroke	log normal	-0.117	0.341	23
HR HF	log normal	-0.478	0.084	23
HR serious adverse events	log normal	0.464	0.067	23

HR minor adverse events	log normal	0.182	0.039	7,8
Disease-specific risk of death	**Distribution**	**Alpha**	**Beta**	**Sources**
Attributable to MI	beta	17.1	2,435	3
Attributable to stroke	beta	1986	89148	4
Attributable to heart failure	beta	1164	148,836	5,6
Probability of serious adverse events	beta	9.88	4,673	23
Probability of minor adverse events/side effects	beta	30.8	103	7
Baseline utilities				
HTN only	**Distribution**	**Alpha**	**Beta**	**Sources**
68-69	beta	3,241	739	14
70-79	beta	2,333	648	14
80 and up	beta	1,142	424	14
Stroke				
68-69	beta	3,252	728	14
70-79	beta	2,348	633	14
80 and up	beta	1,152	414	14
MI				
68-69	beta	3,255	725	14
70-79	beta	2,349	632	14
80 and up	beta	1,152	414	14
HF				
68-69	beta	3,251	729	14
70-79	beta	2,352	629	14
80 and up	beta	1,156	410	14
State-specific disutilities	**Distribution**	**Alpha**	**Beta**	**Sources**
1-disutility for HTN	beta	6908	177	14

1-disutility for MI	beta	234	9.98	14
1-disutility for stroke	beta	322	17.9	14
1-disutility for HF	beta	266	18.0	14
1-disutility for serious adverse events	beta	88.5	11.5	14, assumed a wide distribution
1-disutility for minor adverse events/side effects	beta	99.5	0.5	24, assumed a wide distribution
1-disutility for 2 medications	beta	99.8	0.2	24, assumed a wide distribution

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