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Personalizing Blood Pressure Therapy: Dynamic Treatment Selection and Modification using a Markov Decision Process Model

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Abstract

Objective: Personalized medicine seeks to select and modify treatments based on individual patient characteristics and preferences. We sought to develop an automated strategy to select and modify blood pressure treatments, incorporating the likelihood that patients with different characteristics would benefit from different types of medications and dosages, and the potential severity and impact of different side effects among patients with different characteristics.

Design, setting and participants: We developed a Markov Decision Process (MDP) model to incorporate meta-analytic data and estimate the optimal treatment for maximizing discounted lifetime quality-adjusted life-years (QALYs) based on individual patient characteristics, incorporating medication adjustment choices when a patient incurs side effects. We compared the MDP to current U.S. blood pressure treatment guidelines (the Eighth Joint National Commission, JNC8), and a variant of current guidelines that incorporates results of a major recent trial of intensive treatment ("Intensive JNC8"). We used a microsimulation model of patient demographics, cardiovascular disease risk factors, and side-effect probabilities, sampling from the National Health and Nutrition Examination Survey (2003-2014), to compare the expected population outcomes from adopting the MDP versus guideline-based strategies.

Main outcome measures: The costs and QALYs observed in the dynamic MDP-based treatment ("DMDP"), JNC8, and Intensive JNC8 strategies.

Results: Compared to the JNC8 guideline, the DMDP strategy would be cost-saving from a societal perspective with discounted savings of $1,187 per capita (95% CI: 1,178-1,209) and an estimated discounted gain of 0.06 QALYs per capita (95% CI: 0.04-0.08) among the U.S. adult population. QALY gains would be largely from reductions in severe side effects associated with higher treatment doses later in life. The Intensive JNC8 strategy was dominated by the DMDP strategy.

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Conclusions: A dynamic MDP-based approach can aid decision-making by incorporating meta-analytic evidence to personalize blood pressure treatment and improve overall population health compared to current blood pressure treatment guidelines.

Article summary

Strengths and limitations of this study

- This analysis provides a computational tool to operationalize personalized medicine for blood pressure therapy and determine the optimal treatment for an individual, incorporating complex variety of individual-level covariates, treatment effect modifiers, and risks and benefits of treatment alternatives.
- This framework can approximate optimal treatment decisions in complex and uncertain environments and can be applied to other disease processes
- Based on published data, the health benefits of medications were assumed to be mediated through changes in blood pressure as per current physiologic understandings
- This study used survey data that are subject to recall biases, acceptability biases, and underreporting that may lead to mis-estimation of baseline covariates and limits the analysis to the non-institutionalized US population.

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Introduction

Personalized medicine seeks to select and modify treatments based on individual patient characteristics and preferences.[1] While much of personalized medicine focuses on genetics, an increasing array of studies have suggested that personalized medicine could also assist in overall population health outcomes even when genetics are not considered or relevant, by using large-scale data synthesis approaches to improve medical decision making, particularly when numerous patient features and multi-faceted data must be considered.[2-4] For example, blood pressure therapy guidelines (the Eighth Joint National Committee, JNC8) currently recommend treating large categories of people (e.g., older adults, those with diabetes, and those with chronic kidney disease) to attain specific targets.[5] A few general classes of medications are recommended based on race and co-morbid conditions such as diabetes and chronic kidney disease.

Such simplification poses the dilemma of recommending suboptimal treatment choices with sub-maximal benefit and substantial side-effect risk among some patients, in favor of an approach that may direct appropriate therapies to a majority of patients.[3] Any particular individual patient may have some or all of these features (e.g., features suggesting need for intensive treatment, but also features posing risk for severe side effects), requiring clinicians to judge how intensively to treat patients who have multiple features. The target levels of treatment are themselves also subject to controversy. Lower targets for treatment have also been advocated for some high-cardiovascular disease (CVD)-risk patients following the SPRINT trial in which a target of 120 mmHg for systolic blood pressure was found to reduce CVD event risk among very-high-risk patients[6-8]; yet post hoc analyses found considerable heterogeneity in the

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treatment effects and harms, with some researchers proposing decision rules to find groups of patients more likely to experience benefit or harm from the lower blood pressure target.[9]

Furthermore, side effects of therapy vary among patients with different features, and the complex matrix of different side-effect probabilities is challenging for a clinician to remember and calculate for any given patient.[10] Hence, automated synthesis of complex data to enable personalized therapy may be helpful to maximize benefits and minimize risks among patients.

We developed and tested a generalizable computational strategy to help personalize treatment when multiple treatment options, benefits, and risks must be considered, using a Markov Decision Process (MDP) model—a model in which outcomes are partly under the control of a decision maker and partly based on probabilistic calculations from high-quality meta-analytic data. We applied the model to the selection of blood pressure treatments for each individual in a simulated US population, and compared the benefits and risks expected from clinical application of the strategy to application of current blood pressure treatment guidelines. We open-sourced the model code to permit its replication, application, and potential modification for solving other, similar treatment problems.

Methods

Model overview

We modeled the process of sequentially choosing blood pressure treatment medications with a discrete-time, finite time-horizon MDP, which obtains input data from meta-analyses describing medication choices, their potential treatment effects, and side effects among patients with different characteristics. Our MDP performs optimization using additional data to compute the quality-adjusted life years (QALYs) that would be gained from averted myocardial infarctions or strokes (the primary benefits of lowering blood pressure therapy), or lost to

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specific side effects, over a simulated lifetime.[11, 12] The Appendix contains all input data, equations, and complete technical details consistent with international model reporting guidelines,[13] along with a link to program code for replication and extension of our analysis. Here, we provide an overview of the model's key components (Figure 1 and Table 1).

Model formulation

At each monthly time step $t = 1, \ldots, T$ over a patient's simulated lifetime, the MDP model (Appendix eText 1) is described with four components: state space (S), action space (A), transition probabilities $P(s_{t+1} | s_t, a_t)$, and rewards, $R(s)$.

The state space S, comprising the states at time t (s_t), consisted of demographic information (age, sex, race/ethnicity), the patient's CVD-related covariates (age-, sex- and race-dependent chronic kidney disease status, type 2 diabetes status, lipid profile, and tobacco smoking status), and the patient's health state. A patient could enter one of seven health states (Appendix eFigure 1): (i) no CVD history (no history of myocardial infarction or stroke); (ii) adverse medication side effect but no CVD history; (iii) acute myocardial infarction (MI); (iv) acute stroke; (v) post-CVD event (survived MI or stroke); (vi) adverse medication side effect with a CVD history; or (vii) dead from any cause.

The action space (A) consisted of a finite set of possible actions (treatment decisions). At each state at time t, s_t, three actions, a_t, were possible: the patient could stop a medication treatment, remain on the current medication treatment(s) and dose level(s), or change their medication treatment (by increasing a dosage of a current medication, and/or changing the medication). The objective of the MDP was to determine the optimal treatment policy for a patient, π^*, that maximized the patient's expected discounted QALYs over the patient's simulated lifetime, using a standard 3% annual discount rate (Appendix eText 1).

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Input data

Input data for the model were taken from previously validated risk calculations and meta-analyses of randomized trials. The effect of blood pressure medication on lowering systolic blood pressure (SBP) was estimated as a function of the number of prescribed drugs and the dosage level (full or half dose) of each drug, using equations from previously published studies.[14] In our model, dose levels from 0 (no medication) to 4 (4 drugs at full dose) in increments of 0.5 were modeled: thus, for example, a dose of 0.5 means a half dose of one particular medicine, and 1 means a full dose of one particular medicine. Treatment dose levels were capped at full doses of 4 different medicines, given evidence of no incremental benefit and substantial harm from side effects when escalating therapy beyond 4 full doses[3] (Appendix eText 2).

The probability that a person transitioned from healthy to either MI or stroke was based on equations previously validated in several diverse cohorts containing more than 23,000 subjects, and subsequently against prospective patient-level data on blood pressure and CVD mortality from more than 1 million adults (Appendix eText 3).[15-19] The equations are a function of the set of covariates: age, sex, race/ethnicity (Center for Disease Control and Prevention categories of non-Hispanic White, non-Hispanic Black, Mexican American, and Other), initial systolic and diastolic blood pressures, total and high-density lipoprotein (HDL) cholesterol, tobacco smoking status, current treatment with blood pressure medication, type 2 diabetes status, and previous history of MI or stroke. Covariate values were updated annually to reflect linear age- and secular time-trends. The degree to which a given SBP reduction from a medication at a particular dosage reduced the risk of MI or stroke was calculated based on a prior meta-analysis of randomized trials.[17] Deaths attributable to MI/stroke and competing risks were taken into account as a function of age and sex (Appendix eText 4).[19, 20] The probability of severe adverse

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events (significant side effects leading to clinically significant disability or hospitalization) was determined by a prior meta-analysis, specific to patient covariates, blood pressure medication choice and dosage (Appendix eTable 1).

We simulated 10,000 adults aged 18 to 85 years old over their simulated lifetimes, by repeated sampling with replacement from the correlated covariates in the National Health and Nutrition Examination Survey (NHANES, 2003-2014). We used NHANES survey weights to generate sampling distributions for each covariate,[21] and used multivariate sampling with copulas to capture the correlations among the covariates.[22] We back-calculated the pre-treatment blood pressure for those NHANES subjects reporting current blood pressure treatment, using a previously-published procedure.[3] To ensure face validity, MI and stroke incidence rates were compared through backwards projection while maintaining current blood pressure medications listed in NHANES to years 2003 and 2014, to compare to estimates from the Atherosclerosis Risk in Communities study, the Greater Cincinnati/Northern Kentucky Stroke Study, and independent cohort studies from the National Heart Lung and Blood Institute (NHLBI).[23-25] The validation exercise showed that the model was within 5% absolute error from actual observed incidence rates of MI and stroke (Appendix eFigures 2-3).

Comparative effectiveness analysis

We compared three treatment strategies: (1) JNC8 based on current US guidelines, targeting blood pressure <140/90 mmHg for persons with chronic kidney disease or diabetes, or persons <60 years old, and BP<150/90 mmHg for persons ≥60 years old and without chronic kidney disease or diabetes;[5] (2) Intensive JNC8 (JNC8 modified by results of the recent SPRINT trial), specifically lowering SBP to 120 mmHg among high-risk patients (those with ≥15% 10-year risk of combined MI and stroke) but using the same blood pressure targets as in JNC8 for

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others;[6, 26] and (3) a dynamic MDP-based strategy that determines optimal medication choices based on the MDP (Figure 1). To restrict our analysis to the range of possibilities considered safe and effective, we set the number of blood pressure medications to a maximum of 4 per person, and stopped augmentation of blood pressure treatment if a simulated patient's systolic blood pressure fell below 120 mmHg.[3, 27]

As suggested in JNC8 guidelines, for all treatment strategies, initial blood pressure medication choice included a thiazide, calcium channel blocker (CCB), ACE inhibitor (ACE-I), or angiotensin receptor blocker (ARB) in the general non-Black population, or a thiazide or CCB for the general Black population. In the JNC8 and Intensive JNC8 strategies, if the target blood pressure was not reached within one month, the dosage of the medication was increased, or another medication was added.

We used two outcome metrics to compare the treatment strategies: (i) total discounted QALYs over the lifetime of each simulated individual; (ii) the incremental cost-effectiveness ratio of the dynamic MDP-based (DMDP) strategy versus JNC8, and of Intensive JNC8 versus JNC8.

Cost-effectiveness analysis

Following current cost-effectiveness guidelines[28, 29], costs and QALY estimates were integrated over the life-course for all simulated individuals, starting in 2017. Costs of medications and associated adverse events were obtained from the National Inpatient Sample survey and Red Book (Appendix eTable 2).[30, 31] Annual disease-specific healthcare costs and the disutility of disease states and side effects to calculate QALYs were based on large-scale survey data (Appendix eTable 2).[32, 33] Costs were expressed in 2017 US Dollars using the Consumer Price Index[34],and QALYs were discounted at a 3% annual rate.

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Sensitivity and uncertainty analyses

We performed sensitivity analyses to assess key sources of variability in the outcome estimates, specifically by varying disutility weights for disease states: treatment-related disutility (QALYs per medication per year of treatment associated with serious adverse events) was varied from 0.001 to 0.02. The disutility from CVD events (separately for MI and stroke) was varied across the range from 0.5 to 0.9 based on variations observed in patient survey data.[3, 35-37] We performed uncertainty analyses across all simulations by re-running the full model while repeatedly Monte Carlo sampling with replacement 10,000 times (for 10,000 discrete runs) from the probability distributions of all input parameters.[38]

All analyses were performed in *R* (version 3.2.1, The R Foundation for Statistical Computing, Vienna), with model code available at https://sdr.stanford.edu concurrent with publication.

Results

Dynamic MDP-based treatment (DMDP) strategy vs. JNC8

Over a simulated life course, the dynamic MDP-based treatment (DMDP) strategy tended to treat patients more intensively than JNC8 (Figure 2). The DMDP strategy prescribed 2.34 (95% CI: 2.33-2.34) medication doses per person, versus 2.22 (95% CI: 2.21-2.22) under the JNC8 (Table 2). The greatest increases in dosages from the JNC8 to the DMDP strategy were disproportionately among high-risk individuals aged less than 60 years; patients were treated more intensively earlier in life under the DMDP strategy when their initial 10-year CVD risk was higher (Figure 2 and Table 3). By starting to treat patients more intensively earlier in life based on individual risks and estimated benefits, the DMDP strategy averted more CVD events over

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the course of life, preventing more intensive treatment requirements later in life and thereby saving QALYs (Figure 2 and Table 3).

Treated individuals experienced 19.03 (95% CI: 19.01-19.05) and 18.97 (95% CI: 18.95-18.98) total discounted QALYs per person under the DMDP and JNC8 strategies, respectively. Compared to JNC8, the DMDP strategy gained 0.06 (95% CI: 0.04-0.08) QALYs per person, and was cost-saving with estimated discounted savings of $1,187 (95% CI: 1,168-1,206) per person. The QALY gains would be realized largely from averting CVD events among high-risk individuals by treating them earlier with relatively lower treatment dosages than they would have received later in life.

The projected QALY gains were larger among men than women because larger shifts from the JNC8-recommended to DMDP-recommended treatments tended to intensify men's blood pressure treatments due to their higher risk and higher benefit, and in turn further reduce men's MI and stroke risks (Figure 2 and Appendix eFigure 4).

Dynamic MDP-based treatment (DMDP) strategy vs. Intensive JNC8 strategy

The Intensive JNC8 strategy tended to treat patients more intensively later in life than the DMDP strategy (Figure 2). Over the course of life, individuals under the Intensive JNC8 strategy received 3.18 (95% CI: 3.18-3.19) doses on average per person per day as compared to 2.34 (95% CI: 2.33-2.34) doses under the DMDP strategy. Compared to the DMDP strategy, 63.3% of the simulated population received higher dosages over the course of life under the Intensive JNC8 strategy although the initial 10-year CVD risk of those people was significantly lower than that of people treated more intensively by the DMDP strategy (Appendix eTable 3). By treating based on individual risks, the DMDP strategy tended to treat patients more intensively earlier in life and less intensively at older ages (Figure 2).

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The Intensive JNC8 strategy was dominated by the DMDP strategy. Treated individuals under the Intensive JNC8 strategy experienced 0.04 (95% CI: 0.02-0.06) fewer total discounted QALYs per person than those treated under the DMDP strategy, and at higher costs. By waiting to control blood pressure later in life under the Intensive JNC8 strategy, cumulative exposure to high blood pressure from young adulthood to middle age resulted in higher QALY loss due to CVD events.

Medication choices and SBP levels

Among Black populations, CCBs and ARBs were the most prescribed medications as the first and second medications in both strategies. In addition, thiazides and ACE-Is (or beta-blockers and thiazides for people with prior CVD history) were prescribed the most as the third and fourth medications, respectively, in the DMDP strategy (Appendix eFigure 6).

We measured individuals' SBP levels achieved under each treatment strategy over the simulated period. SBP levels of individuals under the DMDP strategy remained the lowest among individuals aged less than 60 years, at an average of 118.1 mmHg (95% CI: 117.6-118.6) in patients aged 18-39 years old and 126.4 mmHg (95% CI: 125.6-127.2) in patients aged 40-59 years old (Figure 3). For patients older than 60 years old, SBP levels were lowest under the Intensive JNC8 strategy, 139.4 mmHg (95% CI: 138.8-140.0) as compared to 148.9 mmHg (95% CI: 148.0-149.8) under the DMDP strategy.

Results of sensitivity analyses

None of the sensitivity analyses substantially changed our fundamental finding of benefits and cost savings from the DMDP strategy compared to the Intensive JNC8 and JNC8 strategies (Appendix eFigures 7 and 8). The QALY weight for the adverse event states in our base-case analysis was 0.999, which is a conservative estimate for serious adverse effects of

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treatment.[3, 36] When we varied adverse event state QALY weights from 0.98 to 0.999, the lowest estimated QALY gain from the DMDP strategy compared to the JNC8 strategy was 41.0 (95% CI: 21.4-60.6) QALYs per 1000 persons (Appendix eFigure 7). When a QALY weight of 0.98 was assumed for the adverse event states, treated individuals under the Intensive JNC8 did not experience significantly different QALYs than JNC8. With lower QALY weights for adverse events, patients with a CVD history did not have substantially different dose levels under the DMDP strategy (Appendix eFigure 7), but patients without CVD history had lower dose levels than the Intensive JNC8 and JNC8.

Next, we varied MI and stroke QALY weights from 0.5 to 0.9 for either or both of the disease states. The QALY gains from the DMDP strategy compared to the JNC8 strategy ranged from 56.7 (95% CI: 36.4-75.6) to 59.0 (95% CI: 39.4-78.6) QALYs per 1000 persons for MI and from 56.0 (95% CI: 37.1-76.3) to 61.0 (95% CI: 41.4-80.6) QALYs per 1000 persons for stroke (Appendix eFigure 7). Treatment dose levels were not significantly affected by varying QALY weights for CVD (Appendix eFigure 8).

Discussion

Personalizing medical decisions will require considering an increasingly complex variety of individual-level covariates, treatment effect modifiers, and risks and benefits of treatment alternatives. Personalizing decisions is recommended by current CVD management guidelines, as with guidelines for many other conditions, but how to operationalize such guideline statements remains unclear because guidelines generally recommend therapy based on broad categories of features rather than the complex combinations of features that any individual would have.[39] As a result, simple rules of thumb (such as specific blood pressure levels or medication of choice for all people with diabetes) are favored by physicians due to the burden of performing

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complex risk/benefit calculations at each step of the treatment decision-making process.[3, 40] Personalizing decisions may therefore be made more optimal through the use of automated computational strategies to incorporate individual patient data into individualized treatment recommendations. While several studies have previously suggested that blood pressure therapy should involve calculations of patient risks and benefits, this is the first time—to our knowledge—that a systematic, comprehensive, and automated calculation approach has been proposed to achieve this objective.[3, 4]

We developed an MDP-based model to optimize treatment of blood pressure medication and dose selection, based on currently best-available meta-analytic data and risk calculations. While there remains considerable uncertainty in any model-based treatment selection, we found that even when repeatedly sampling over uncertainty ranges of blood pressure treatment benefit and risk, a substantial improvement could be made over current blood pressure management guidelines not only for individuals, but also for the overall population. Our study suggests that initiating blood pressure management earlier for young and middle-aged adults with prehypertension substantially reduces MI and/or stroke occurrences over the course of life. This is particularly notable in light of doubts that personalized medicine can improve population health.[41, 42] We open-sourced our code to permit replication and extension to other disease processes that similarly involve risk/benefit calculations among a large number of potential treatments with different treatment effects and side-effect probabilities among different types of patients, as is currently the case with type 2 diabetes, cancer, and HIV.[43, 44]

As with any modeling exercise, our study is limited by the quality of its input data and assumptions. First, we modeled the effects of blood pressure treatment medication based on published data, assuming that the health benefits of medications were mediated through changes

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in blood pressure as per current physiologic understandings. Second, we used data from NHANES, which are subject to the limitations of survey studies, including recall biases, acceptability biases, and underreporting that may lead to mis-estimation of baseline covariates and limits the analysis to the civilian (non-institutionalized) US population.[45] Third, although we performed uncertainty analyses by sampling from distributions around the input parameter data sources, we cannot capture all possible uncertainties in the model. We focused on myocardial infarction and stroke because of high-quality, validated risk equations for predicting these outcomes and their risk reduction through therapy. Although congestive heart failure and kidney diseases may also be averted, we did not model them due to the lack of robust and validated risk equations; however, their impact is considered proportional to the impact on MI and stroke[3], and thus should not affect our comparative effectiveness analysis. Ignoring these potential benefits makes our cost-effectiveness estimates conservative.

The next logical step for analysis is to prospectively test the MDP-based model in clinical settings to identify safety, adoptability, and impact on patient outcomes. An additional logical step for future research is to identify whether QALY values co-vary meaningfully among individuals as a function of their risk, age, and prior treatment. Use of personalized QALYs would enable more personalized decision-making rather than assuming that QALY weights of CVD outcomes or serious adverse events are consistent across the population. For example, some persons may favor lower risk of side effects than CVD events if they are concerned about short-term suffering rather than long-term mortality (e.g., if they are near the end of life).

While these remain important topics for future research, our current findings indicate that blood pressure treatment policies informed by a Markov Decision Process framework may

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improve patient outcomes compared to the use of standardized target-based guidelines, by accounting for individual-patient covariates in treatment decision-making processes.

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Table 1. Model Parameters and Sources

Parameters	Source
Population size of demographic cohorts	NHANES 2003-2014
Risk of MI or stroke by demographic group (Appendix eText 3)	Model-based estimates from meta-analysis data[17-19]
Baseline MI history prevalence (Appendix eTable 4)	NHANES 2003-2014
Baseline stroke history prevalence (Appendix eTable 5)	NHANES 2003-2014
Baseline hypertension medication use prevalence (Appendix eTable 6)	NHANES 2003-2014
Baseline systolic blood pressure (Appendix eTable 7)	NHANES 2003-2014
Baseline total cholesterol (Appendix eTable 8)	NHANES 2003-2014
Baseline HDL cholesterol (Appendix eTable 9)	NHANES 2003-2014
Baseline smoking prevalence (Appendix eTable 10)	NHANES 2003-2014
Baseline Type 2 diabetes prevalence (Appendix eTable 11)	NHANES 2003-2014
Baseline chronic kidney disease prevalence (Appendix eTable 12)	NHANES 2003-2014
MI or stroke mortality rate (Appendix eText 4)	Model calibration to national data[17-19]
All-cause mortality rate	CDC[20]

NHANES=National Health and Nutrition Examination Survey; MI=myocardial infarction; CDC=Center for Disease Control and Prevention; HDL=High-density lipoprotein

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Table 2. Differences in Treatment (Mean (se)), and Cost-Effectiveness Analysis

Treatment Strategy	Treatment Dose	MI events (%)	Stroke events (%)	Total QALYs	Total cost ($)	Incremental QALYs vs. JNC8	Incremental cost ($) vs. JNC8	ICER vs. JNC8
JNC8	2.22 (0.001)	33.21 (0.11)	35.60 (0.11)	18.97 (0.01)	16,459 (10.68)	-	-	
Intensive JNC8	3.18 (0.001)	32.79 (0.11)	34.99 (0.11)	18.99 (0.01)	17,385 (11.52)	0.02	926	Dominated
Dynamic MDP-based (DMDP)	2.34 (0.002)	29.99 (0.11)	32.63 (0.11)	19.03 (0.01)	15,272 (9.81)	0.06	-1,187	Cost-saving

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Table 3. Efficiency Table (DMDP vs. JNC8 Strategies)

	Treated similarly* by both JNC8 and DMDP strategies	People treated more intensively by DMDP strategy	People treated more intensively byJNC8 strategy
% of population	12.4	47.8	39.8
Mean initial 10-y CVD risk	13.4	15.2	13.1
Mean post-10 years of treatment 10-year CVD risk	14.1	14.7	14.7
QALY loss saved from CVD events, per 1000 patients **treated, compared to JNC8**	1.39	3.01	1.54
QALY loss saved from adverse events, per 1000 patients **treated, compared to JNC8**	-0.03	-0.09	-0.02
Total QALYs saved, per 1000 patients **treated, compared to JNC8**	40.0	74.9	44.6

DMDP = dynamic Markov Decision Process-Based treatment strategy; JNC8 = Joint National Commission Series 8 treatment strategy

*"Treated similarly" was defined as rounded mean treatment dose level over lifetime being the same between the JNC8 and DMDP strategies

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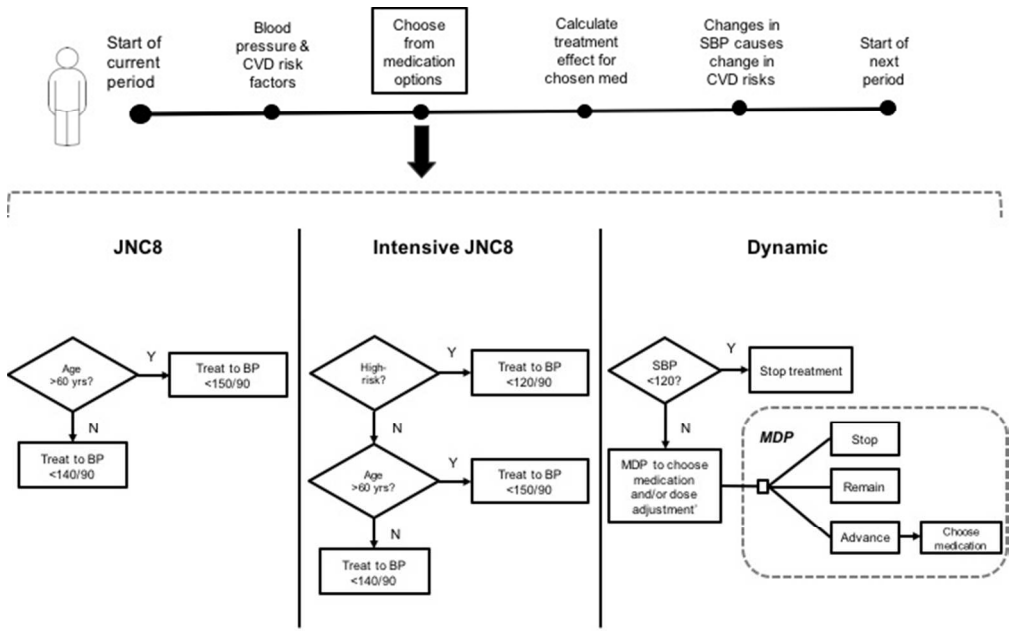

Figure 1. Model schematic
* "High-risk" was defined the same as SPRINT and ACCORD enrollment eligibility criteria except for type 2 diabetes status

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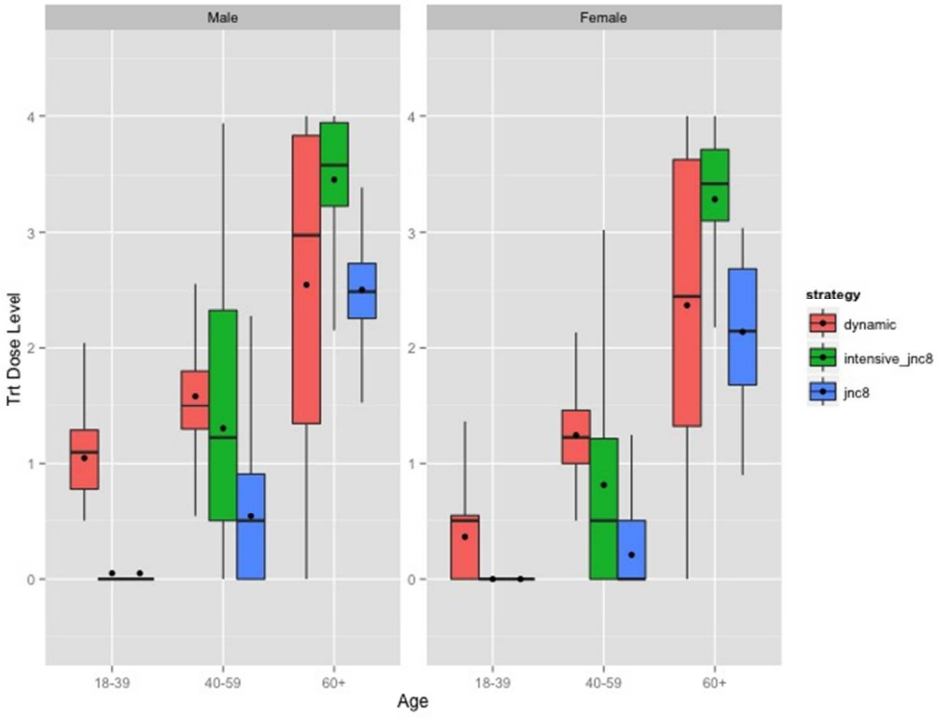

Figure 2. Treatment dose levels received by individuals under each treatment strategy

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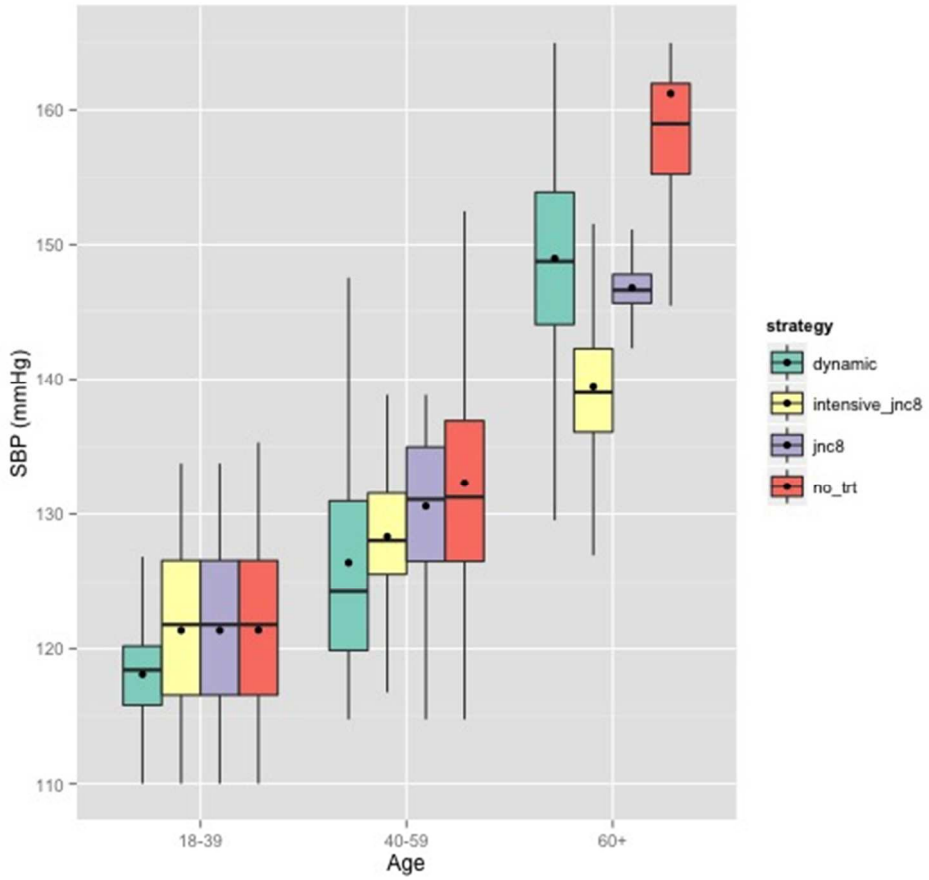

Figure 3. Mean systolic blood pressure (SBP) levels of individuals achieved under each treatment strategy

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PERSONALIZING BLOOD PRESSURE THERAPY: DYNAMIC TREATMENT SELECTION AND MODIFICATION USING A MARKOV DECISION PROCESS MODEL

APPENDIX

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eText 2. Effects of blood pressure medication on blood pressure and CVD risks
eText 3. Risk of myocardial infarction (MI) or stroke
eText 4. Mortality after myocardial infarction (MI) or stroke

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eFigure 4. Total QALY gains over patient lifetimes of the Intensive JNC8 strategy and the Dynamic MDP-based strategy compared to the JNC8 strategy
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eFigure 6. Comparison of medications selected in dynamic MDP-based approach vs. current guidelines
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eText 1. Markov Decision Process (MDP) formulation

Here we present the formulation of the MDP model. The simulation code is available at https://sdr.stanford.edu/. The MDP model is characterized by a state space, action space, transition probabilities, and rewards. A patient may enter one of 7 health states, as illustrated in eFigure 1: (1) Well; (2) Adverse event without CVD history; (3) MI; (4) Stroke; (5) Post CVD; (6) Adverse event with CVD history; (7) death. Model notation is shown in eTable 13.

The objective of the MDP is to determine the optimal treatment strategy π* for a single patient that maximizes the patient's expected discounted QALYs over a simulated time horizon. Patients can take up to 4 different medications from among the following: angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), beta-blocker, calcium channel Blocker (CCB), thiazide diuretic. The treatment dose scale is as follows:

0 – No treatment
0.5 – One drug, ½ dose
1 – One drug, 1 dose
1.5 – Two drugs, ½ doses
2 – Two drugs, 1 dose each
2.5 – Three drugs, ½ doses
3 – Three drugs, 1 dose each
3.5 – Four drugs, ½ doses
4 – Four drugs, 1 dose each

Transition probabilities $P_a(s, s')$, are functions of: the patient's post-treatment CVD risk, $r_a(s)$ → $r_a(s) = RR(s)*r(s)$; the likelihood of death from a CVD event, $\rho(s)$; the likelihood of non-CVD death, $\varphi(s)$; the likelihood of side effects from treatment, $\beta_{a,m}(s)$.

The transition probabilities $P_a(s, s')$ are updated in every time step (i.e., every month). At each time step, individuals are faced with either continuing with the current treatment option or advancing to the next level. When transitioning from s to s' state, rewards are given by:

$$R_a(s, s') = Q_a(s, s')$$

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At each time step, π will contain the solution and $V(s)$ will contain the discounted sum of the rewards to be earned (on average) by following that solution from state s. The Bellman value function gives the maximized expected QALYs when in state s:

$$V(s) = \sum_{s'} P_a(s,s')(R_a(s,s') + \lambda V(s'))$$

The optimal policy maximizes the sum of expected QALYs over the time horizon:

$$\pi(s) = argmax_a\{\sum_{s'} P_a(s,s')(R_a(s,s') + \lambda V(s'))\}.$$

eText 2. Effects of hypertension medication on blood pressure and CVD risks

The effect of blood pressure medications on lowering blood pressure as a function of dose was estimated based on a meta-analysis of 35 short-term randomized placebo controlled trials of blood pressure-lowering drugs in fixed dose,[1] which showed that the five main classes of blood pressure-lowering drugs produce similar reductions in blood pressure. The blood pressure lowering effect of the drugs was estimated as a function of treatment dose and pretreatment blood pressure.

The estimated effect of one drug at standard dose in lowering blood pressure from a pretreatment blood pressure P was (9.1+0.10(P−154)) systolic blood pressure. The estimated blood pressure reduction for higher standard dose was calculated by applying these equations to each drug in turn, allowing for the effect of the first in lowering pretreatment blood pressure for the second, and the second for the third, and so on. The blood pressure reductions from half standard doses were (R+n*0.078(P−150)) systolic blood pressure, where R is the blood pressure reduction at 150 mm Hg systolic blood pressure, n is the number of drugs, and P is the pretreatment blood pressure. Using these equation yields the following estimates of R:

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Number of drugs at standard dose	*R*
One drug half standard dose	6.7
Two drugs half standard dose	13.3
Three drugs half standard dose	19.9
Four drugs half standard dose	26.5

Given SBP changes from blood pressure medication, the relative risk reduction of MI and stroke was estimated using previously published equations (equations (1) and (2) below).[2] The equations were estimated by fitting curves to data from a meta-analysis of prospective patient-level data on blood pressure and CVD mortality.[3]

Slope MI = -1.1009E-05 age^2 + 8.6305 E -04 age + 3.5176 E -02 (1)
Relative risk of MI = 2^(change in SBP*slope MI)

Slope stroke = -2.5946E -05 age^2 + 2.3052E -03 age + 2.2168E -02 (2)
Relative risk of stroke = 2^(change in SBP*slope stroke)

eText 3. Risk of myocardial infarction (MI) or stroke

We used validated equations of monthly risks of MI and stroke estimated by fitting exponential curves to data on age- and sex-specific incidence of first MI and stroke from the Framingham Heart Study (1980-2003), published by the National Heart, Lung, and Blood Institute.[2, 4]

Given no history of MI (x = age in years), monthly risk of MI is:

Male: $y = 0.0001 * e^{0.0312x}$ (3)
Female: $y = 8E-06 * e^{0.0599x}$ (4)

Given no history of stroke (x = age in years), monthly risk of stroke is:

Male: $y = 9E-06 * e^{0.0622x}$ (5)
Female: $y = 3E-06 * e^{0.0741x}$ (6)

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Given history of CVD, the risk of MI or stroke without a history of CVD was multiplied by a constant with a mean of 2, standard deviation 1.0204, gamma distribution (shape=3.84166, scale=0.520608).

To account for other CVD risk factors, we adopted a previously published approach in which weights are assigned to each individual based on the following risk factors used in the Framingham risk equations[5, 6]: age, total cholesterol, HDL cholesterol, hypertension treatment status, smoking, and diabetes. Individual Framingham risks were divided by the mean Framingham risk of each cohort (defined by age, sex, race, and income), then used to weight each individual's baseline MI and stroke risk equations, equations (3)-(6). The Framingham risk equations are as follows:

For males:

Individual_FHS_risk = (1-0.88936)*exp((3.06117*log(age)+1.12370*log(total_cholesterol)-0.93263*log(HDL_cholesterol)+1.99881*log(SBP_treated)+1.93303*log(SBP_untreated)+0.65451*smoking+0.57367*diabetes)- 23.9802)

For females:

Individual_FHS_risk = (1-0.95012)*exp((2.32888*log(age)+1.20904*log(total_cholesterol)-0.70833*log(HDL_cholesterol)+2.82263*log(SBP_treated)+2.76157*log(SBP_untreated)+0.52873*smoking+0.69154*diabetes)-26.1931)

$$\text{Weights assigned to individual} = \frac{\text{Individual FHS risk}}{\text{Mean FHS risk of each cohort}}$$

eText 4. Mortality after myocardial infarction (MI) or stroke

We used validated equations of age- and sex-specific risk of mortality after MI and stroke developed by fitting exponential curves to the ratio of incidence of fatal event to total incidence of event. Data on fatal MI and total incidence of MI was obtained from the Framingham Heart Study. The ratio of fatal stroke to stroke incidence was obtained from the Cardiovascular Health Study.[2, 4] This yields the following estimated mortality risks.

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Risk of mortality after MI (x = age in years):

Male: $y = 0.0289 * e^{0.0269x}$

Female: $y = 0.0004 * e^{0.0706x}$

Risk of mortality after stroke (x = age in years):

Male: $y = 0.0003 * e^{0.0782x}$

Female: $y = 0.0034 * e^{0.0428x}$

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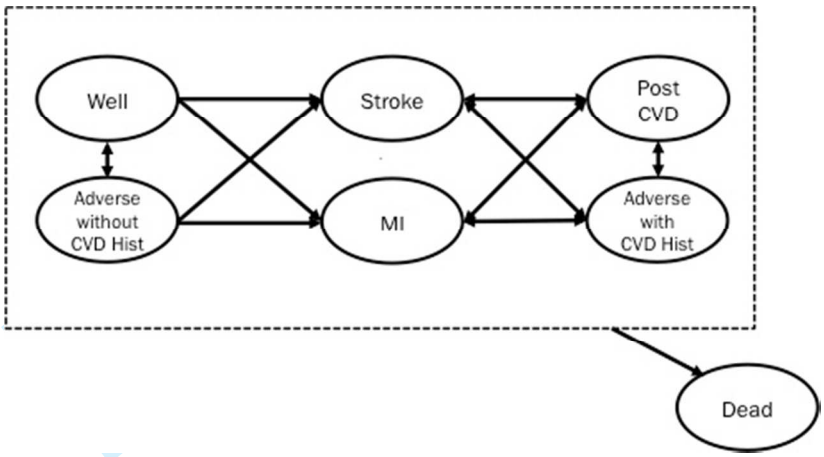
eFigure 1. Schematic of health states in Markov Decision Process



CVD: Cardiovascular disease; CVD Hist: CVD History

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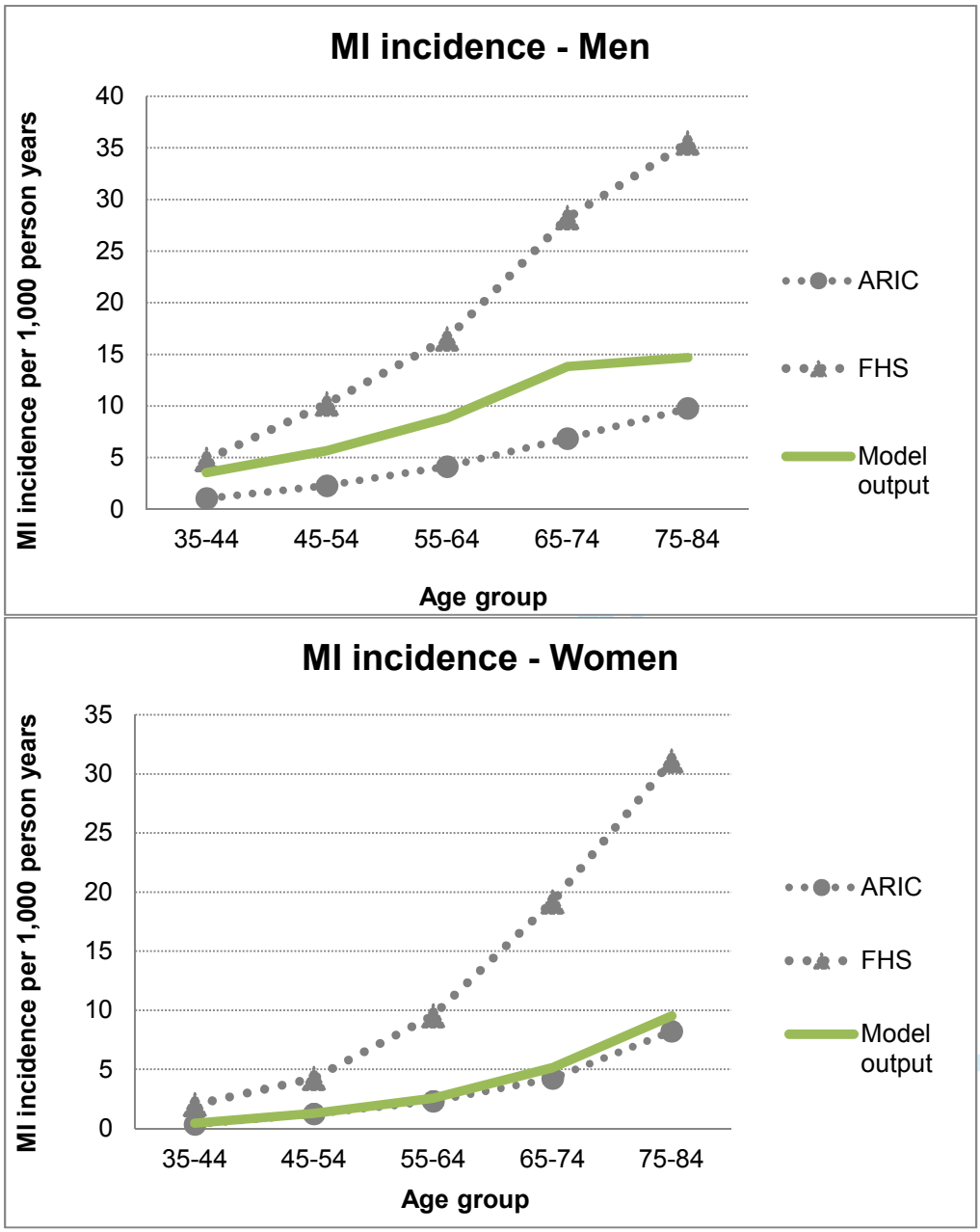
eFigure 2. Calibration results: MI incidence. We considered our targets were met if the projected incidence fell within the interval between the estimates from Framingham Heart Study (FHS) and Atherosclerosis Risk in Communities study (ARIC) which are, respectively more-inclusive and less-inclusive measures of composite CVD outcomes



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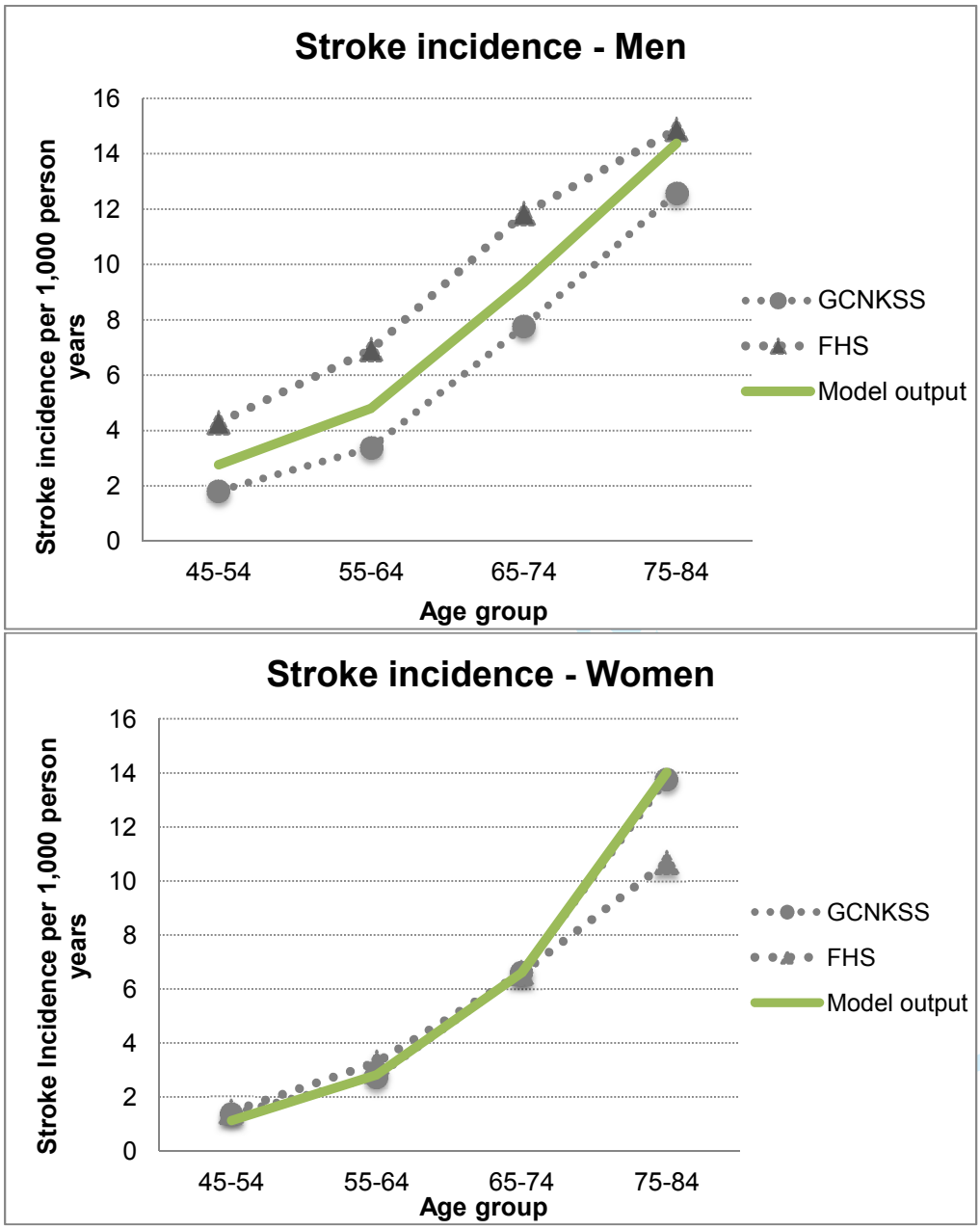
eFigure 3. Calibration results: stroke incidence. We considered our targets were met if the projected incidence fell within the interval between the estimates from Framingham Heart Study (FHS) and the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS)



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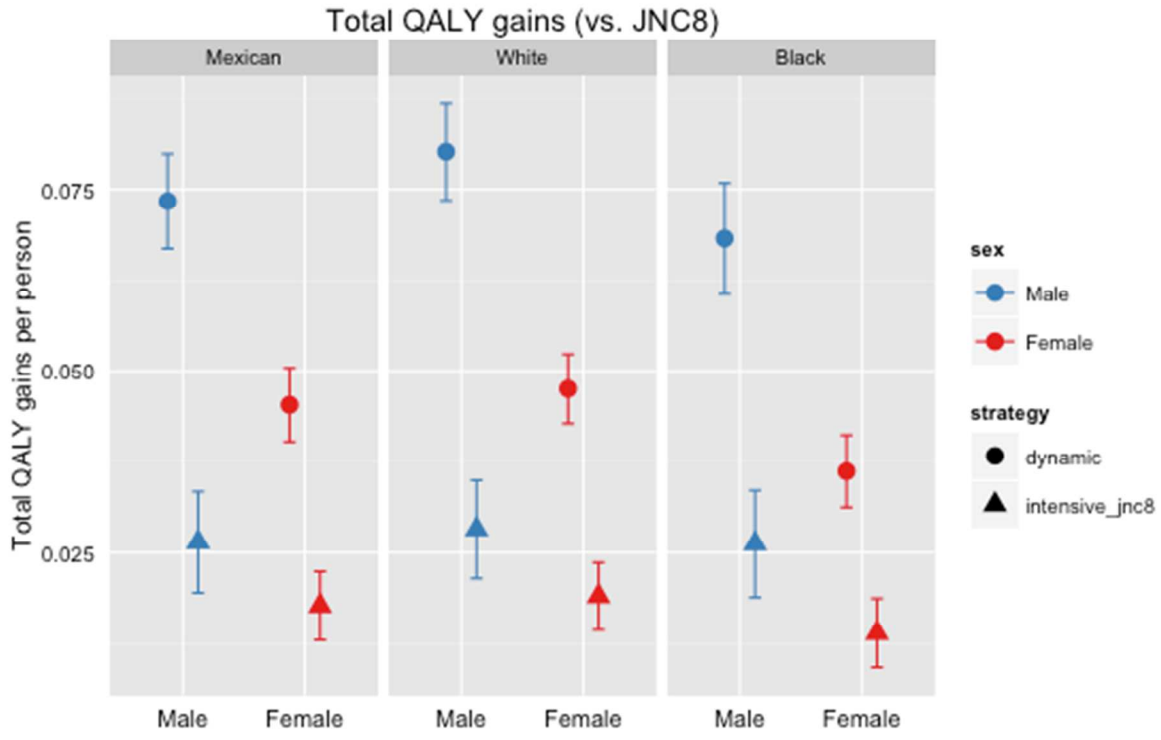
eFigure 4. Total QALY gains over patient lifetimes of the Intensive JNC8 strategy and the Dynamic MDP-based strategy compared to the JNC8 strategy



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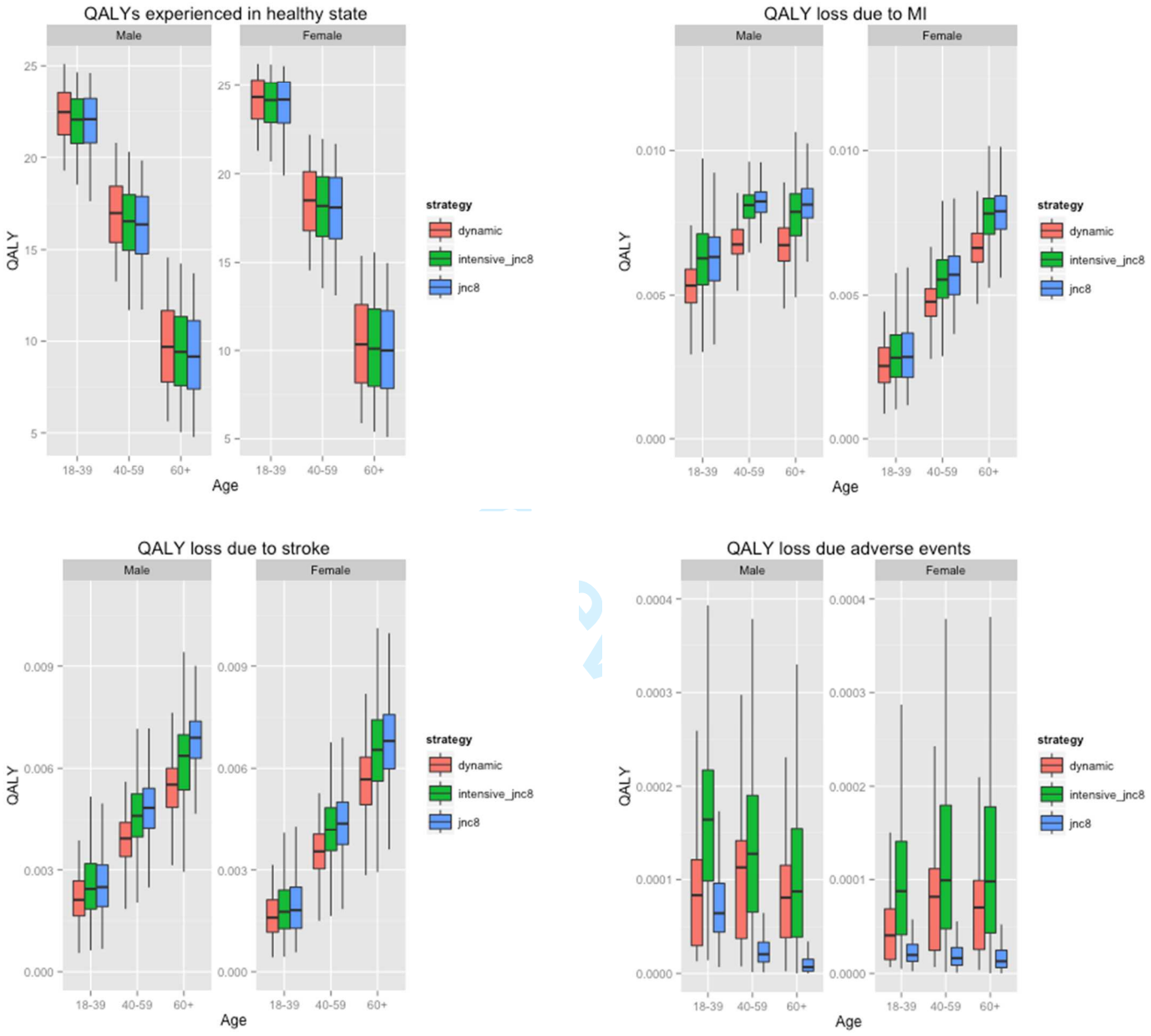
eFigure 5. QALYs in each disease state over patient lifetimes



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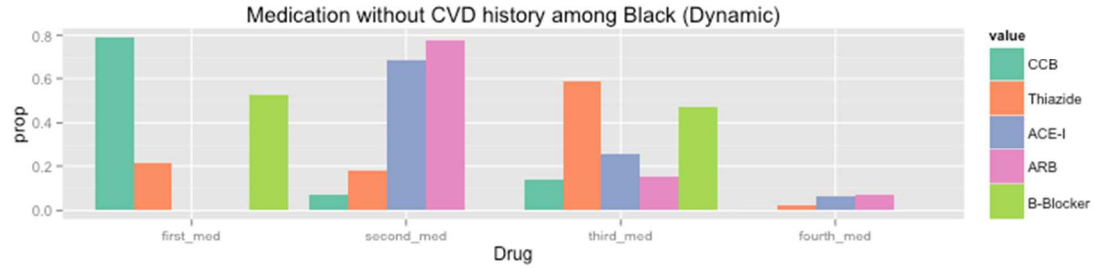
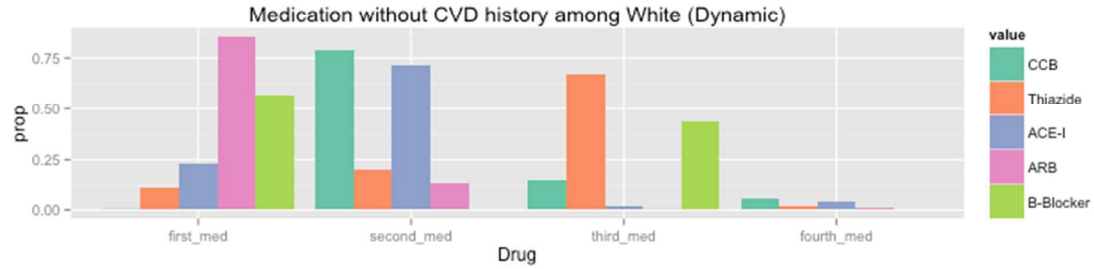
eFigure 6. Comparison of medications selected in dynamic MDP-based approach vs. current guidelines

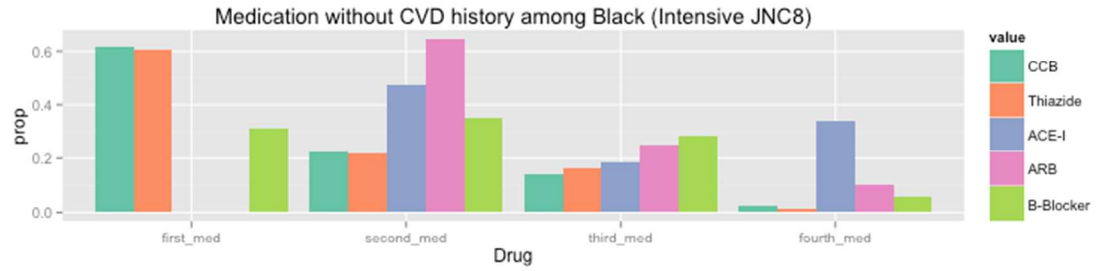
Without CVD History

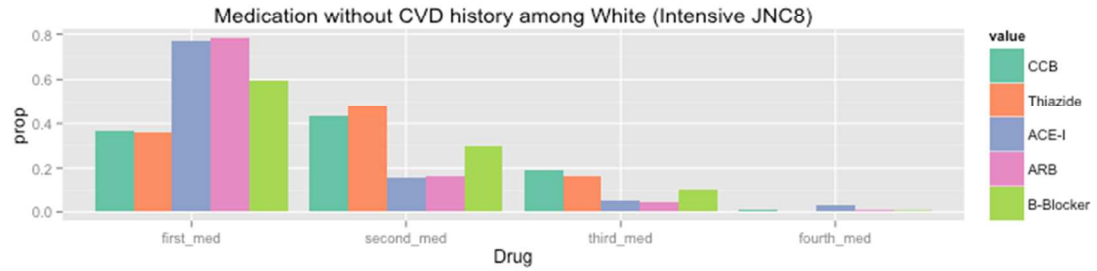
Dynamic





JNC8





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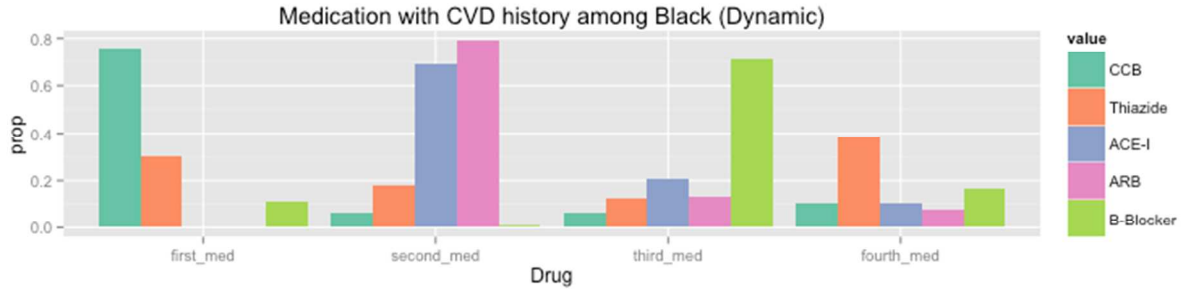
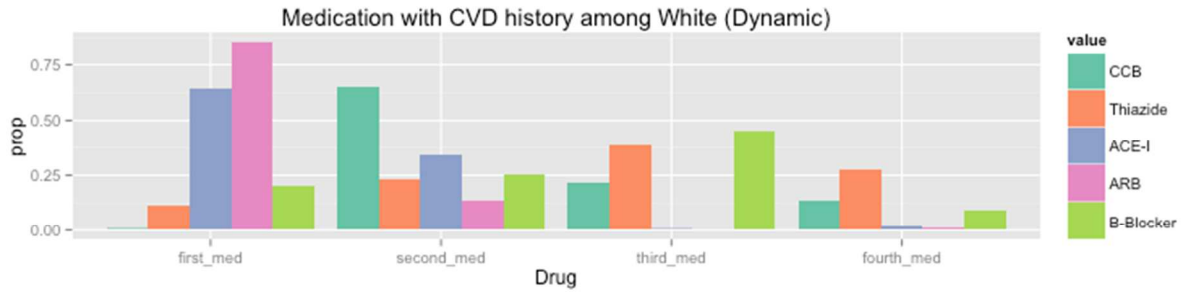
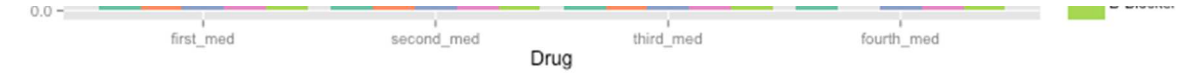
With CVD History

Dynamic





JNC8



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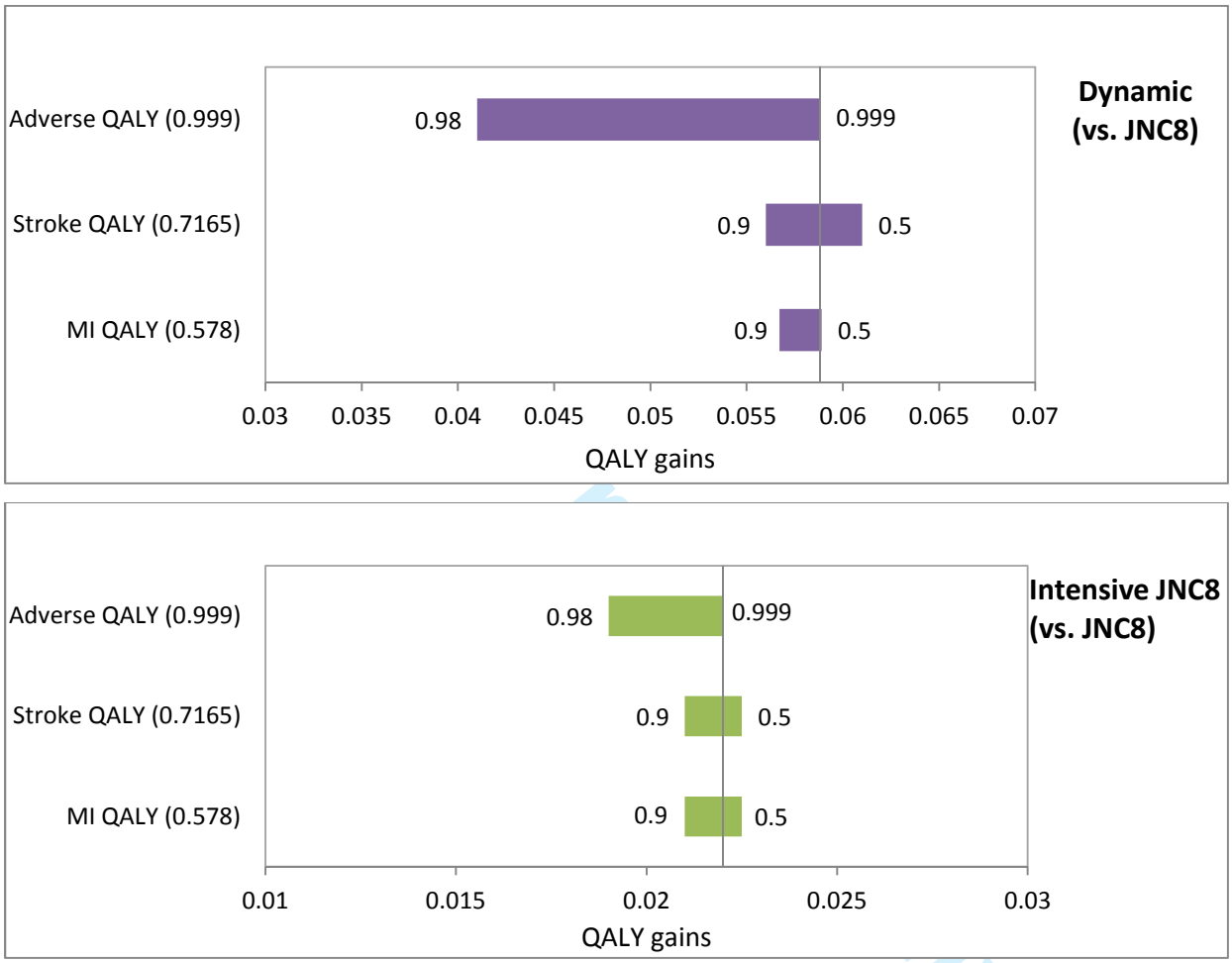
eFigure 7. Sensitivity analysis: QALY gains from the dynamic MDP-based approach and the Intensive JNC8 strategy (vs. JNC8)

The vertical lines represent the QALY gains in the base case analysis, and the horizontal bars represent the variation of the QALY gains given variations of parameters. The numbers at each end of the bars represent the lower and upper bounds of the value used for each parameter.



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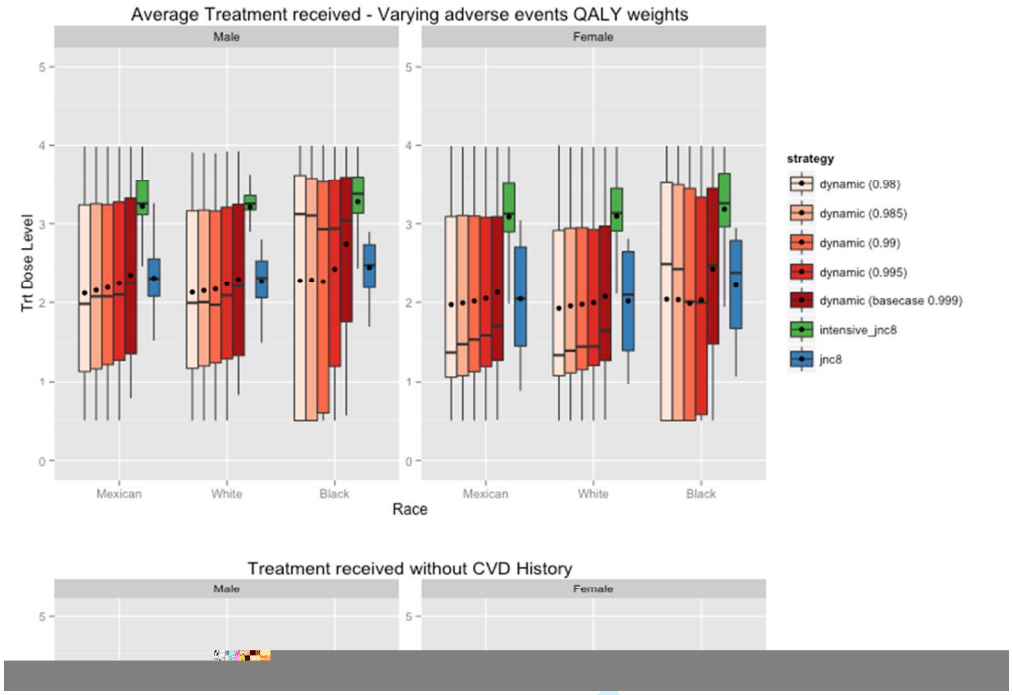
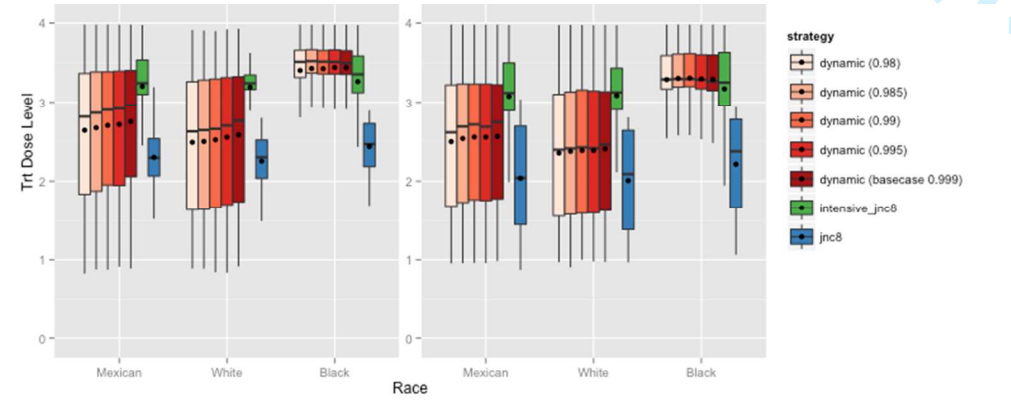
eFigure 8. Sensitivity analyses: Treatment dose levels given variation in QALY weights
Adverse event QALY weights





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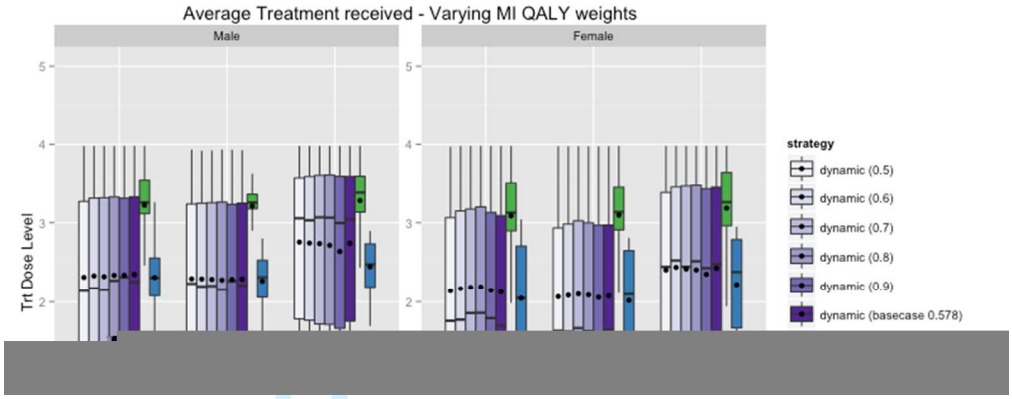
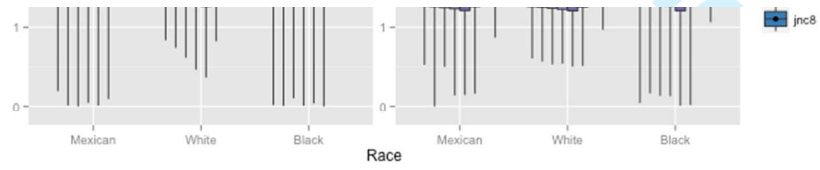
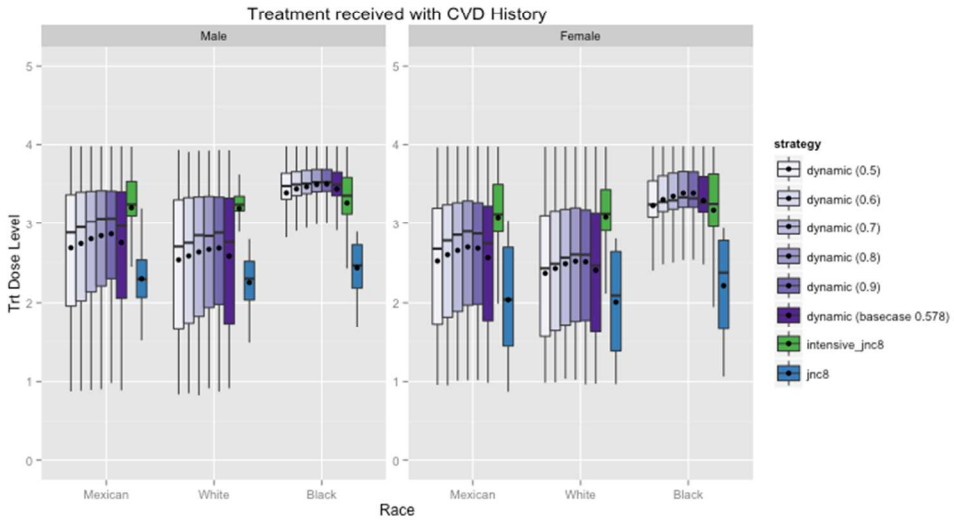
MI QALY weights







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Stroke QALY weights

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eTable 1. Risk of Adverse Events from Medications: Percentage of Patients with One or More Symptoms Attributable to Treatment

Medication	Half dose		Standard dose		Twice Standard	
	Mean	SD	Mean	SD	Mean	SD
ACE- I	3.9	3.88	3.9	2.24	3.9	2.09
ARB	-1.8	4.28	0	1.79	1.9	3.83
Beta-blocker	5.5	2.6	7.5	1.79	9.4	2.6
CCB	1.6	2.65	8.3	1.79	14.9	2.95
Thiazide	2	2.14	9.9	1.68	17.8	3.21

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eTable 2. Quality-of-Life and Cost Estimates for Disease States and Adverse Events

By disease states and adverse events, mean (sd)

Disease states	Quality of life	Sources
MI	0.578	[7, 8]
Stroke	0.7165	[7-9]
Post CVD	0.9	[7, 8]
Adverse event	0.999	[8]

Disease states	Annual cost	Sources
MI	$44,267	[9]
Stroke	$23,254 (1400)	[9]
Post CVD	$5,208 (356)	[10]
Adverse event	(see below)	

Annual costs of medications and associated adverse events [9, 11, 12]

Dose	Antihypertensive drug costs	Costs of adverse events*
0.5 standard doses	gamma(1.24, rate = 0.01)	$65.92
1.0 standard dose	gamma(1.66, rate = 0.01)	$131.4
1.5 standard doses	gamma(0.216, rate = 0.001)	$162.63
2.0 standard doses	gamma(0.238, rate = 0.001)	$193.87
2.5 standard doses	gamma(0.298, rate = 0.001)	$225.93
3.0 standard doses	gamma(0.357, rate = 0.001)	$258.05
3.5 standard doses	gamma(0.430, rate = 0.001)	$258.05
4.0 standard doses	gamma(0.496, rate = 0.001)	$258.05

* Costs of adverse events were estimated based on hospitalization cost - average cost (used for infrequent hospitalized drug-related adverse events) and high costs (used for rare hospitalized drug-related adverse events) – and incidence rates of serious adverse effects of medication (common, infrequent, and rare).

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eTable 3. Comparison of Dynamic vs. Intensive JNC8 Strategies

	Treated similarly by both Intensive JNC8 and Dynamic strategies	People treated more intensively by Dynamic strategy	People treated more intensively by Intensive JNC8 strategy
% of population	19.1	17.6	63.3
Mean initial 10-year CVD risk	14.5	18.6	12.7
Mean post-10 years of treatment 10-year CVD risk	14.6	14.8	14.6
QALY loss saved from CVD events, per 1000 patients treated, compared to Intensive JNC8	1.85	2.17	1.25
QALY loss saved from adverse events, per 1000 patients treated, compared to Intensive JNC8	0.03	-0.04	0.07
Total QALYs saved, per 1000 patients treated, compared to Intensive JNC8	43.4	46.8	31.7

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eTable 4. Baseline MI History Prevalence (%)

		Age					
Sex	**Race**	**20-39**	**20-39**	**40-59**	**40-59**	**60-85**	**60-e85**
		Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Male	Mexican	0.00	NA	0.72	0.25	6.92	1.04
	NH White	0.21	0.04	2.31	0.18	15.42	0.48
	NH Black	0.00	NA	4.43	0.61	12.11	0.75
Female	Mexican	0.00	NA	1.26	0.29	4.11	0.60
	NH White	1.34	0.22	1.32	0.16	8.71	0.38
	NH Black	0	NA	0	NA	5.91	0.06

eTable 5. Baseline Stroke History Prevalence (%)

		Age					
Sex	**Race**	**20-39**	**20-39**	**40-59**	**40-59**	**60-85**	**60-e85**
		Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Male	Mexican	0.00	NA	1.91	1.89	9.43	3.94
	NH White	0.14	0.13	0.42	0.24	6.51	1.48
	NH Black	0.00	NA	1.98	1.72	12.61	3.76
Female	Mexican	0.00	NA	1.51	8.66	2.68	2.30
	NH White	1.05	1.04	1.69	0.61	7.95	1.72
	NH Black	0.33	0.32	4.49	2.32	8.02	2.95

eTable 6. Baseline Hypertension Medication Use Prevalence (%)

		Age					
Sex	**Race**	**20-39**	**20-39**	**40-59**	**40-59**	**60-85**	**60-e85**
		Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Male	Mexican	1.46	1.48	9.75	5.26	41.66	8.53
	NH White	3.95	1.49	14.25	2.35	52.41	2.41
	NH Black	5.76	1.41	33.54	4.48	62.41	3.91
Female	Mexican	7.88	5.24	6.47	3.48	47.86	10.54
	NH White	0.81	0.64	24.70	3.30	54.23	3.42
	NH Black	9.48	3.41	43.57	4.95	75.36	6.23

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eTable 7. Baseline Systolic Blood Pressure (mmHg)

		Age					
Sex	**Race**	**20-39**	**20-39**	**40-59**	**40-59**	**60-85**	**60-e85**
		Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Male	Mexican	121.4	1.2	124.1	3.2	135.1	7.6
	NH White	120.5	1.2	124.4	1.2	131.1	1.1
	NH Black	123.5	1.0	128.5	1.4	136.8	1.2
Female	Mexican	110.6	1.4	120.3	2.4	138.5	3.9
	NH White	109.9	0.7	121.2	1.1	135.3	1.3
	NH Black	113.8	1.3	128.5	1.9	140.4	1.9

eTable 8. Baseline Total Cholesterol (mmol/L)

		Age					
Sex	**Race**	**20-39**	**20-39**	**40-59**	**40-59**	**60-85**	**60-e85**
		Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Male	Mexican	179.1	5.4	208.8	6.8	187.8	8.1
	NH White	191.5	4.4	206.4	2.1	187.8	1.4
	NH Black	182.3	3.3	190.8	5.0	184.9	4.6
Female	Mexican	187.2	5.6	208.9	6.7	208.6	9.5
	NH White	189.8	2.9	209.6	2.9	208.5	2.4
	NH Black	182.9	2.8	201.4	3.9	206.9	5.6

eTable 9. Baseline HDL Cholesterol (mmol/L)

		Age					
Sex	**Race**	**20-39**	**20-39**	**40-59**	**40-59**	**60-85**	**60-e85**
		Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Male	Mexican	44.8	1.8	52.8	3.7	48.4	4.4
	NH White	47.3	1.1	49.1	0.8	51.2	0.6
	NH Black	49.5	1.5	54.9	2.7	53.0	0.7
Female	Mexican	58.7	2.4	55.7	4.1	53.3	2.4
	NH White	58.5	1.0	60.0	0.9	63.0	1.0
	NH Black	59.4	1.6	62.4	1.7	64.7	3.2

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eTable10. Baseline Smoking Prevalence (%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-e85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	26.7	6.1	18.4	10.6	16.9	4.3
	NH White	30.9	3.1	24.1	3.6	11.9	2.8
	NH Black	27.6	4.5	35.5	6.8	22.1	5.0
Female	Mexican	9.5	4.5	26.2	9.0	9.9	3.1
	NH White	27.2	4.5	16.4	3.0	12.7	2.5
	NH Black	23.7	6.6	22.7	4.6	15.1	4.5

eTable 11. Baseline Type 2 Diabetes Prevalence (%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-e85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	0	NA	19.4	7.3	37.2	9.3
	NH White	1.3	0.7	4.9	1.3	14.7	2.2
	NH Black	5.1	1.5	14.2	5.7	32.9	5.0
Female	Mexican	2.7	1.2	5.2	2.1	30.7	4.8
	NH White	2.8	1.7	4.3	1.1	12.9	1.6
	NH Black	2.6	1.6	15.8	4.5	34.1	3.8

eTable 12. Baseline Chronic Kidney Disease (CKD) Prevalence (%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-e85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	10.5	3.3	2.6	2.3	19.4	5.9
	NH White	14.5	2.0	17.6	2.1	14.7	2.9
	NH Black	1.4	0.7	4.2	2.1	10.6	3.3
Female	Mexican	25.8	6.9	22.5	6.6	48.5	4.4
	NH White	23.2	4.3	41.1	2.4	42.8	3.2
	NH Black	6.9	1.7	6.8	1.8	13.6	3.4

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eTable 13. MDP Model Notation

Variable	Description
t	Time index; $t = 0,1,\ldots,T$
$d \in D$	Treatment dose options A. A=(1,…,9)
$m \in M$	Number of treatment drugs M. M=(1,…,4)
$b_{min} \in R+$	Minimum allowable SBP
$g \in G$	Multidimensional state of the patient represented by the number of remaining decision epochs in the planning horizon, risk factors including demographic information for the patient (e.g. age, sex, smoking status), and CVD competing risk factors (pretreatment SBP, DBP, total cholesterol, HDL cholesterol, smoking status, hypertension treatment status, diabetes status, CVD history) n = 0,..., N, the number of remaining decision epochs p represents patient demographic information (age, sex, race, income) $b \in$ R+ denotes the pretreatment SBP c represents patient CVD competing risk factors. $s \in [1, \ldots,7]$ denotes the patient health state $g = (n; p; b; c; s)$
$RR(s) \in [0; 1]$	Relative-risk factor when in state s
$r(s) \in [0; 1]$	Patient's pretreatment risk of a CVD event in state s
$r_a(s) \in [0; 1]$	Patient's post treatment risk of a CVD event in state s with action a; $D(s)*r(s)$
$P_a(s, s')$	Transition probabilities from state s to s'
$\varphi(s) \in [0; 1]$	Probability of death from non-CVD cause given the patient's post-treatment CVD risk when in state s
$\rho(s) \in [0; 1]$	Probability of death from a CVD event when in state s, given that the patient had a CVD event
$\beta_{a,m}(s) \in [0; 1]$	Probability of experiencing side effects (adverse events) in state s
$Q_a(s, s')$	QALYs associated with transition from s to s'
λ	Discount rate for costs and health benefits

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Personalizing Blood Pressure Therapy: Dynamic Treatment Selection and Modification Using a Markov Decision Process Model

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SEC: study conception and design, statistical analysis, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript; **MLB:** study conception and design, analysis and interpretation of data, critical revision of the manuscript; **SB**: study conception and design, statistical analysis, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript, obtained funding.

Abstract word count: 296; Text word count: 3942

Keywords: blood pressure; cardiovascular disease; personalized medicine

Abstract

Objective: Personalized medicine seeks to select and modify treatments based on individual patient characteristics and preferences. We sought to develop an automated strategy to select and modify blood pressure treatments, incorporating the likelihood that patients with different characteristics would benefit from different types of medications and dosages, and the potential severity and impact of different side effects among patients with different characteristics.

Design, setting and participants: We developed a Markov Decision Process (MDP) model to incorporate meta-analytic data and estimate the optimal treatment for maximizing discounted lifetime quality-adjusted life-years (QALYs) based on individual patient characteristics, incorporating medication adjustment choices when a patient incurs side effects. We compared the MDP to current U.S. blood pressure treatment guidelines (the Eighth Joint National Committee, JNC8), and a variant of current guidelines that incorporates results of a major recent trial of intensive treatment ("Intensive JNC8"). We used a microsimulation model of patient demographics, cardiovascular disease risk factors, and side-effect probabilities, sampling from the National Health and Nutrition Examination Survey (2003-2014),

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to compare the expected population outcomes from adopting the MDP versus guideline-based strategies.

Main outcome measures: Costs and QALYs for the MDP-based treatment ("MDPT"), JNC8, and Intensive JNC8 strategies.

Results: Compared to the JNC8 guideline, the MDPT strategy would be cost-saving from a societal perspective with discounted savings of $1,187 per capita (95% CI: 1,178-1,209) and an estimated discounted gain of 0.06 QALYs per capita (95% CI: 0.04-0.08) among the U.S. adult population. QALY gains would largely accrue from reductions in severe side effects associated with higher treatment doses later in life. The Intensive JNC8 strategy was dominated by the MDPT strategy.

Conclusions: An MDP-based approach can aid decision-making by incorporating meta-analytic evidence to personalize blood pressure treatment and improve overall population health compared to current blood pressure treatment guidelines.

Article summary

Strengths and limitations of this study

- This analysis provides a computational tool to operationalize personalized medicine for blood pressure therapy and determine the optimal treatment for an individual, incorporating a complex variety of individual-level covariates, treatment effect modifiers, and risks and benefits of treatment alternatives.
- This framework can approximate optimal treatment decisions in complex and uncertain environments and can be applied to other disease processes.
- Based on published data, the health benefits of medications were assumed to be mediated through changes in blood pressure as per current physiologic understanding.

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- This study used survey data that are subject to recall biases, acceptability biases, and underreporting that may lead to mis-estimation of baseline covariates, and limits the analysis to the non-institutionalized U.S. population.

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Introduction

Personalized medicine seeks to select and modify treatments based on individual patient characteristics and preferences.[1] While much of personalized medicine focuses on genetics, an increasing number of studies have suggested that personalized medicine could also assist in improving overall population health outcomes even when genetics are not considered or relevant, by using large-scale data synthesis approaches to improve medical decision-making, particularly when numerous patient features and multi-faceted data must be considered.[2-4] For example, blood pressure therapy guidelines (the Eighth Joint National Committee, JNC8) currently recommend treating large categories of people (e.g., older adults, those with diabetes, and those with chronic kidney disease) to attain specific targets.[5] A few general classes of medications are recommended based on race and co-morbid conditions such as diabetes and chronic kidney disease.

Such simplification poses the dilemma of recommending suboptimal treatment choices with sub-maximal benefit and substantial side-effect risk among some patients, in favor of an approach that may direct appropriate therapies to a majority of patients.[3] Any particular individual patient may have some or all of these features (e.g., features suggesting the need for intensive treatment, but also features posing risk for severe side effects), requiring clinicians to judge how intensively to treat patients who have multiple features. The target levels of treatment are themselves also subject to controversy. Lower targets for treatment have been advocated for some high-cardiovascular disease (CVD)-risk patients following the SPRINT trial in which a target of 120 mmHg for systolic blood pressure was found to reduce CVD event risk among very-high-risk patients[6-8]; yet post hoc analyses found considerable heterogeneity in the treatment effects and harms, with some researchers proposing decision rules to find groups of patients more likely to experience benefit or harm from the lower blood pressure target.[9]

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Furthermore, side effects of therapy vary among patients with different features, and the complex matrix of different side-effect probabilities is challenging for a clinician to remember and calculate for any given patient.[10] Hence, automated synthesis of complex data to enable personalized therapy may be helpful to maximize benefits and minimize risks among patients.

We developed and tested a generalizable computational strategy to help personalize treatment when multiple treatment options, benefits, and risks must be considered, using a Markov Decision Process (MDP) model—a model in which outcomes are partly under the control of a decision maker and partly based on probabilistic calculations from high-quality meta-analytic data. Prior work suggests that personalizing optimal treatment policies using an MDP framework could improve patient health outcomes compared to JNC7 treatment guidelines.[11] This prior work focuses on assessing the impact of the MDP-based policies on certain cohorts of patients, not on population health. Our study advances this prior literature by incorporating large-scale meta-analytic and network meta-analytic data sources, providing a full life-course simulation to evaluate long-term impact, and using population-representative data to assess the overall national implications of personalized blood pressure treatment selection. We open-sourced the model code to permit its replication, application, and potential modification for solving other, similar treatment problems.

Methods

Model overview

We modeled the process of sequentially choosing blood pressure treatment medications with a discrete-time, finite time-horizon MDP, which obtains input data from meta-analyses describing medication choices, their potential treatment effects, and side effects among patients with different characteristics. Accounting for patient's characteristics, our MDP performs optimization using additional data to compute the quality-adjusted life years (QALYs) that would be gained from averted myocardial

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infarctions (MIs) or strokes (the primary benefits of lowering blood pressure), or lost to specific side effects, over a simulated lifetime.[12, 13] The Appendix contains all input data, equations, and complete technical details consistent with international model reporting guidelines,[14] along with a link to program code for replication and extension of our analysis. Here, we provide an overview of the model's key components (Figure 1, Table 1).

Model formulation

At each monthly time step $t = 1, \ldots, T$ over a patient's simulated lifetime, the MDP model (Appendix eText 1) is described with four components: state space (S), action space (A), transition probabilities $P(s_{t+1} | s_t, a_t)$, and rewards, $R(s)$. The cycle length of one month was chosen to be in accordance with current clinical guidelines and with the timing of observations for SBP reduction in randomized trials used to inform the model, and to capture rapid response in blood pressure to antihypertension medication.[6, 15]

The action space (A) consisted of a finite set of possible actions (treatment decisions). For each state s_t at time t, three actions, a_t, were possible: the patient could stop a medication treatment, remain on the current medication treatment(s) and dose level(s), or change medication treatment (by increasing a dosage of a current medication, and/or changing the medication) (Appendix eFigure 1). The state space S, comprising the states at time t (s_t), consisted of demographic information (age, sex, race/ethnicity), the patient's CVD-related covariates (age-, sex- and race-dependent chronic kidney disease status, type 2 diabetes status, lipid profile, and tobacco smoking status), and the patient's health state. A patient could enter one of seven health states (Appendix eFigure 2): (i) no CVD history (no history of myocardial infarction or stroke); (ii) adverse medication side effect but no CVD history; (iii) acute myocardial infarction (MI); (iv) acute stroke; (v) post-CVD event (survived MI or stroke); (vi) adverse medication side effect with a CVD history; or (vii) dead from any cause. Transition probabilities

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P(s_{t+1}| s_t, a_t) for a certain action were determined from the action and the state, which contains a patient's characteristics (demographic information and CVD-related covariates) in the current state.

The objective of the MDP was to determine the optimal treatment policy for a patient, π^*, that maximized the patient's expected discounted QALYs over the patient's simulated lifetime, using a standard 3% annual discount rate (Appendix eText 1).

Input data

Input data for the model were taken from previously validated risk calculations and meta-analyses of randomized trials. The effect of blood pressure medication on lowering systolic blood pressure (SBP) was estimated as a function of the number of prescribed drugs and the dosage level (full or half dose) of each drug, using equations from previously published studies.[16] In our model, dose levels from 0 (no medication) to 4 (4 drugs at full dose) in increments of 0.5 were modeled: thus, for example, a dose of 0.5 means a half dose of one particular medicine, and 1 means a full dose of one particular medicine. Patients were allowed to take up to full doses of 4 different medicines, given evidence of no incremental benefit and substantial harm from side effects when escalating therapy beyond 4 full doses (Appendix eText 2).[3]

The probability that a person transitioned from healthy to either MI or stroke was based on equations previously validated in several diverse cohorts containing more than 23,000 subjects, and subsequently against prospective patient-level data on blood pressure and CVD mortality from more than 1 million adults (Appendix eText 3).[17-21] The equations are a function of the set of covariates: age, sex, race/ethnicity (Centers for Disease Control and Prevention categories of non-Hispanic White, non-Hispanic Black, Mexican American, and Other), initial systolic and diastolic blood pressures, total and high-density lipoprotein (HDL) cholesterol, tobacco smoking status, current treatment with blood pressure medication, type 2 diabetes status, and previous history of MI or stroke. Covariate values were

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updated annually to reflect linear age- and secular time-trends. The degree to which a given SBP reduction from a medication at a particular dosage reduced the risk of MI or stroke was calculated based on a prior meta-analysis of randomized trials.[19] Deaths attributable to MI/stroke and competing risks were taken into account as a function of age and sex (Appendix eText 4).[21, 22] The probability of severe adverse events (significant side effects leading to clinically significant disability or hospitalization) was determined by a prior meta-analysis, specific to patient covariates, blood pressure medication choice and dosage (Appendix eTable 1).

We simulated 10,000 adults aged 18 to 85 years old over their lifetimes, by repeated sampling with replacement from the correlated covariates in the National Health and Nutrition Examination Survey (NHANES, 2003-2014, *N*= 74,501). We used NHANES survey weights to generate sampling distributions for each covariate,[23] and used multivariate sampling with copulas to capture the correlations among the covariates.[24] To estimate untreated blood pressure for those NHANES participants on antihypertensive medication, we back-calculated the pretreatment blood pressure for those reporting current blood pressure treatment, using a previously published procedure.[3] To ensure face validity, MI and stroke incidence rates were compared through backwards projection while maintaining current blood pressure medications listed in NHANES to years 2003 and 2014, to compare to estimates from the Atherosclerosis Risk in Communities study, the Greater Cincinnati/Northern Kentucky Stroke Study, and independent cohort studies from the National Heart Lung and Blood Institute (NHLBI).[25-27] The validation exercise showed that the model was within 5% absolute error from actual observed incidence rates of MI and stroke (Appendix eFigures 3-4).

Comparative effectiveness analysis

We compared three treatment strategies: (1) JNC8 based on current US guidelines, targeting blood pressure <140/90 mmHg for persons with chronic kidney disease or diabetes, or persons <60

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years old, and BP<150/90 mmHg for persons ≥60 years old and without chronic kidney disease or diabetes;[5] (2) Intensive JNC8 (JNC8 modified by results of the recent SPRINT trial), specifically lowering SBP to 120 mmHg among high-risk patients (those with ≥15% 10-year risk of combined MI and stroke) but using the same blood pressure targets as in JNC8 for others;[6, 15] and (3) an MDP-based treatment (MDPT) strategy that determines optimal medication choices based on the MDP (Figure 1). To restrict our analysis to the range of possibilities considered safe and effective, we set the number of blood pressure medications to a maximum of 4 per person, and stopped augmentation of blood pressure treatment if a simulated patient's systolic blood pressure fell below 120 mmHg.[3, 28]

As suggested in JNC8 guidelines, for all treatment strategies, initial blood pressure medication choice included a thiazide, calcium channel blocker (CCB), ACE inhibitor (ACE-I), or angiotensin receptor blocker (ARB) in the general non-Black population, or a thiazide or CCB for the general Black population. In the JNC8 and Intensive JNC8 strategies, if the target blood pressure was not reached within one month, the dosage of the medication was increased, or another medication was added.

We used two outcome metrics to compare the treatment strategies: (i) total discounted QALYs over the lifetime of each simulated individual; (ii) the incremental cost-effectiveness ratio of the MDPT strategy versus JNC8, and of Intensive JNC8 versus JNC8.

Cost-effectiveness analysis

Following current cost-effectiveness guidelines[29, 30], costs and QALY estimates were integrated over the life-course for all simulated individuals, starting in 2017. Costs of medications and associated adverse events were obtained from the National Inpatient Sample survey and Red Book (Appendix eTable 2).[31, 32] Annual disease-specific healthcare costs and the disutility of disease states and side effects to calculate QALYs were based on large-scale survey data (Appendix eTable 2).[33, 34] Costs were

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expressed in 2017 US Dollars using the Consumer Price Index[35],and QALYs were discounted at 3% annually.

Sensitivity and uncertainty analyses

We performed sensitivity analyses to assess key sources of variability in the outcome estimates, specifically by varying disutility weights for disease states: treatment-related disutility (QALYs per medication per year of treatment associated with serious adverse events) was varied from 0.001 to 0.02. The disutility from CVD events (separately for MI and stroke) was varied across the range from 0.5 to 0.9 based on variations observed in patient survey data.[3, 36-38] We performed uncertainty analyses across all simulations by re-running the full model while repeatedly Monte Carlo sampling with replacement 10,000 times (thus 10,000 discrete runs) from the probability distributions of all input parameters.[39]

All analyses were performed in *R* (version 3.2.1, The R Foundation for Statistical Computing, Vienna), with model code available at https://sdr.stanford.edu concurrent with publication.

Results

MDP-based treatment (MDPT) strategy vs. JNC8

Over a simulated life course, the MDPT strategy tended to treat patients more intensively than JNC8 (Figure 2). The MDPT strategy prescribed 2.34 (95% CI: 2.33-2.34) medication doses per person, versus 2.22 (95% CI: 2.21-2.22) under JNC8 (Table 2). The greatest increases in dosages from the JNC8 to the MDPT strategy were among high-risk individuals aged less than 60 years; patients were treated more intensively earlier in life under the MDPT strategy when their initial 10-year CVD risk was higher (Figure 2 and Table 3). These increases in dosages were more prominent among Blacks (eFigure 5). By starting to treat patients more intensively earlier in life based on individual risks and estimated benefits,

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the MDPT strategy averted more CVD events over the course of life, preventing more intensive treatment requirements later in life and thereby saving QALYs (eFigure 6 and Table 3).

Treated individuals experienced 19.03 (95% CI: 19.01-19.05) and 18.97 (95% CI: 18.95-18.98) total discounted QALYs per person under the MDPT and JNC8 strategies, respectively. Compared to JNC8, the MDPT strategy gained 0.06 (95% CI: 0.04-0.08) QALYs per person, and was cost-saving with estimated discounted savings of $1,187 (95% CI: 1,168-1,206) per person. The QALY gains would be realized largely from averting CVD events among high-risk individuals by treating them earlier with relatively lower treatment dosages than they would have received later in life.

The projected QALY gains were larger among men than women because larger shifts from the JNC8-recommended to MDPT-recommended treatments tended to intensify men's blood pressure treatments due to their higher risk and higher benefit, and in turn further reduce men's MI and stroke risks (Appendix eFigures 6-7).

MDP-based treatment (MDPT) strategy vs. Intensive JNC8 strategy

The Intensive JNC8 strategy tended to treat patients more intensively later in life than the MDPT strategy (Figure 2). Over the course of life, individuals under the Intensive JNC8 strategy received 3.18 (95% CI: 3.18-3.19) doses on average per person per day as compared to 2.34 (95% CI: 2.33-2.34) doses under the MDPT strategy. Compared to the MDPT strategy, 63.3% of the simulated population received higher dosages over the course of life under the Intensive JNC8 strategy although the initial 10-year CVD risk of those people was significantly lower than that of people treated more intensively by the MDPT strategy (Appendix eTable 3). By treating based on individual risks, the MDPT strategy tended to treat patients more intensively earlier in life and less intensively at older ages (Figure 2).

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The Intensive JNC8 strategy was dominated by the MDPT strategy. Treated individuals under the Intensive JNC8 strategy experienced 0.04 (95% CI: 0.02-0.06) fewer total discounted QALYs per person than those treated under the MDPT strategy, and at higher costs. By waiting to control blood pressure later in life under the Intensive JNC8 strategy, cumulative exposure to high blood pressure from young adulthood to middle age resulted in higher QALY loss due to CVD events (Appendix eFigure 6).

Medication choices and SBP levels

Among Black populations, CCBs and ARBs were the most prescribed medications as the first and second medications in both strategies. In addition, thiazides and ACE-Is (or beta-blockers and thiazides for people with prior CVD history) were prescribed the most as the third and fourth medications, respectively, in the MDPT strategy (Appendix eFigure 8).

We measured individuals' SBP levels achieved under each treatment strategy over the simulated period. SBP levels of individuals under the MDPT strategy remained the lowest among individuals aged less than 60 years, at an average of 118.1 mmHg (95% CI: 117.6-118.6) in patients aged 18-39 years old and 126.4 mmHg (95% CI: 125.6-127.2) in patients aged 40-59 years old (Figure 3). For patients older than 60 years old, SBP levels were lowest under the Intensive JNC8 strategy, 139.4 mmHg (95% CI: 138.8-140.0) as compared to 148.9 mmHg (95% CI: 148.0-149.8) under the MDPT strategy.

Results of sensitivity analyses

None of the sensitivity analyses substantially changed our fundamental finding of benefits and cost savings from the MDPT strategy compared to the Intensive JNC8 and JNC8 strategies (Appendix eFigures 9 and 10). The QALY weight for the adverse event states in our base-case analysis was 0.999, which is a conservative estimate for serious adverse effects of treatment.[3, 37] When we varied adverse event state QALY weights from 0.98 to 0.999, the lowest estimated QALY gain from the MDPT strategy

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compared to the JNC8 strategy was 41.0 (95% CI: 21.4-60.6) QALYs per 1000 persons (Appendix eFigure 9). When a QALY weight of 0.98 was assumed for the adverse event states, treated individuals under the Intensive JNC8 did not experience significantly different QALYs than JNC8. With lower QALY weights for adverse events, patients with a CVD history did not have substantially different dose levels under the MDPT strategy (Appendix eFigure 9), but patients without CVD history had lower dose levels than under Intensive JNC8 and JNC8.

Next, we varied MI and stroke QALY weights from 0.5 to 0.9 for either or both of the disease states. The QALY gains from the MDPT strategy compared to the JNC8 strategy ranged from 56.7 (95% CI: 36.4-75.6) to 59.0 (95% CI: 39.4-78.6) QALYs per 1000 persons for MI and from 56.0 (95% CI: 37.1-76.3) to 61.0 (95% CI: 41.4-80.6) QALYs per 1000 persons for stroke (Appendix eFigure 9). Treatment dose levels were not significantly affected by varying QALY weights for CVD (Appendix eFigure 10).

Discussion

Personalizing medical decisions will require considering an increasingly complex variety of individual-level covariates, treatment effect modifiers, and risks and benefits of treatment alternatives. Personalizing decisions is recommended by current CVD management guidelines, as with guidelines for many other conditions, but how to operationalize such guideline statements remains unclear because guidelines generally recommend therapy based on broad categories of features rather than the complex combinations of features that any individual would have.[40] As a result, simple rules of thumb (such as specific blood pressure levels or medication of choice for all people with diabetes) are favored by physicians due to the burden of performing complex risk/benefit calculations at each step of the treatment decision-making process.[3, 41] Personalizing decisions may therefore be made more optimal through the use of automated computational strategies to incorporate individual patient data into individualized treatment recommendations. While several studies have previously suggested that blood

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pressure therapy should involve calculations of patient risks and benefits, using a Markov simulation model, this is the first time—to our knowledge—that a systematic, comprehensive, and automated calculation approach has been proposed to achieve this objective by incorporating patient heterogeneity in risk factors and responses to treatment (probabilistically), and recommending detailed treatment suggestions (doses and types of medication).[3, 4] From a clinical perspective, our analysis advances the literature beyond the decision of whether to treat high blood pressure because both type and dosage of medication are critical decision points.

We developed an MDP-based model to optimize treatment of blood pressure medication and dose selection, based on currently best-available meta-analytic data and risk calculations. While there remains considerable uncertainty in any model-based treatment selection, we found that even when repeatedly sampling over uncertainty ranges of blood pressure treatment benefit and risk, a substantial improvement could be made over current blood pressure management guidelines not only for individuals, but also for the overall population. Our study suggests that initiating blood pressure management earlier for young and middle-aged adults with prehypertension substantially reduces MI and/or stroke occurrences over the course of life; the cumulative QALY benefit from the MDP-based approach was primarily from long-term chronic outcomes of high blood pressure leading to long-term sequelae of MI and strokes. This is particularly notable in light of doubts that personalized medicine can improve population health.[42, 43] We open-sourced our code to permit replication and extension to other disease processes that similarly involve risk/benefit calculations among a large number of potential treatments with different treatment effects and side-effect probabilities among different types of patients, as is currently the case with type 2 diabetes, cancer, and HIV.[44, 45]

As with any modeling exercise, our study is limited by the quality of its input data and assumptions. First, we modeled the effects of blood pressure treatment medication based on published data, assuming that the health benefits of medications were mediated through changes in blood

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pressure as per current physiologic understanding. Second, we used data from NHANES, which are subject to the limitations of survey studies, including recall biases, acceptability biases, and underreporting that may lead to mis-estimation of baseline covariates and limits the analysis to the civilian (non-institutionalized) US population.[46] Third, we did not incorporate compliance/adherence parameters in the model because our purpose in this model is to compare how a change in guidelines from the current guidelines to the MDP-based strategy would affect overall population-level outcomes under the ideal treatment condition. Adding in a compliance/adherence parameter would simply linearly scale the outcomes to the proportion of patients who adhere, unless we have further data from [not yet extant] randomized trials suggesting that patients would adhere differently to treatment regimens found using the MDP-based approach than to regimens identified under the current guidelines. We suggest that such randomized trials and real-world studies should be performed now that a proof-of-concept model is available, to gather empirical data comparing adherence rates and observed outcomes between the MDP-based and current guideline approaches. Fourth, although we performed uncertainty analyses by sampling from distributions around the input parameter data sources, we cannot capture all possible uncertainties in the model. We focused on MI and stroke because of high-quality, validated risk equations for predicting these outcomes and their risk reduction through therapy. Although congestive heart failure and kidney diseases may also be averted, we did not model them due to the lack of robust and validated risk equations; however, their impact is considered proportional to the impact on MI and stroke[3], and thus should not affect our comparative effectiveness analysis. Ignoring these potential benefits makes our cost-effectiveness estimates conservative. Lastly, we chose MDP over other reinforcement learning approaches due to its simplicity and flexibility. Perfect knowledge about a patient's states under MDP is a strong assumption, but we chose to use MDP since it is often tractable to solve (exact solution) and relatively easy to specify, and because CVD health states are objectively observable by clinicians under nearly all circumstances (unlike with some other diseases). Partially

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observed MDPs (POMDPs) are more complex than MDPs and are often computationally intractable to solve. Future research could explore the use of a POMDP for determining personalized blood pressure treatment guidelines.

The next logical step for analysis is to prospectively test the MDP-based model in clinical settings to identify safety, adoptability, and impact on patient outcomes. Existing clinical guidelines are typically easy for clinicians to interpret because they involve univariate decisions. To make use of the MDP-based approach, clinicians would need to shift conceptually from a univariate to a multivariate decision process as well as accept computationally complex "black box" results (as they do currently with some imaging and pathological diagnostic guidelines). An additional logical step for future research is to identify whether QALY values co-vary meaningfully among individuals as a function of their risk, age, and prior treatment. Use of personalized QALYs would enable more personalized decision-making rather than assuming that QALY weights of CVD outcomes or serious adverse events are consistent across the population. For example, some persons may favor lower risk of side effects than CVD events if they are concerned about short-term suffering rather than long-term mortality (e.g., if they are near the end of life).

While these remain important topics for future research, our current findings indicate that blood pressure treatment policies informed by a Markov Decision Process framework may improve patient outcomes compared to the use of standardized target-based guidelines, by accounting for individual-patient covariates in treatment decision-making processes, and are likely to be cost-saving compared to current guidelines.

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Table 1. Model Parameters and Sources

Parameters	Source
Population size of demographic cohorts	NHANES 2003-2014
Risk of MI or stroke by demographic group (Appendix eText 3)	Model-based estimates from meta-analysis data[19-21]
Baseline MI history prevalence (Appendix eTable 4)	NHANES 2003-2014
Baseline stroke history prevalence (Appendix eTable 5)	NHANES 2003-2014
Baseline hypertension medication use prevalence (Appendix eTable 6)	NHANES 2003-2014
Baseline systolic blood pressure (Appendix eTable 7)	NHANES 2003-2014
Baseline total cholesterol (Appendix eTable 8)	NHANES 2003-2014
Baseline HDL cholesterol (Appendix eTable 9)	NHANES 2003-2014
Baseline smoking prevalence (Appendix eTable 10)	NHANES 2003-2014
Baseline Type 2 diabetes prevalence (Appendix eTable 11)	NHANES 2003-2014
Baseline chronic kidney disease prevalence (Appendix eTable 12)	NHANES 2003-2014
MI or stroke mortality rate (Appendix eText 4)	Model calibration to national data[19-21]
All-cause mortality rate	CDC[22]

NHANES = National Health and Nutrition Examination Survey; MI = myocardial infarction; CDC = Centers for Disease Control and Prevention; HDL = High-density lipoprotein

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Table 2. Differences in Treatment (Mean (se)), and Cost-Effectiveness Analysis

Treatment strategy	Treatment dose	MI events (%)	Stroke events (%)	Total QALYs	Total cost ($)	Incremental per person QALYs vs. JNC8	Incremental per person cost ($) vs. JNC8	ICER vs. JNC8
JNC8	2.22 (0.001)	33.21 (0.11)	35.60 (0.11)	18.97 (0.01)	16,459 (10.68)	-	-	
Intensive JNC8	3.18 (0.001)	32.79 (0.11)	34.99 (0.11)	18.99 (0.01)	17,385 (11.52)	0.02	926	Dominated
MDP-based treatment (MDPT)	2.34 (0.002)	29.99 (0.11)	32.63 (0.11)	19.03 (0.01)	15,272 (9.81)	0.06	-1,187	Cost-saving

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Table 3. Comparison of MDPT vs. JNC8 Strategy

	People treated similarly* by both JNC8 and MDPT strategies	People treated more intensively by MDPT strategy	People treated more intensively by JNC8 strategy
% of population	12.4	47.8	39.8
Mean initial 10-year CVD risk	13.4	15.2	13.1
Mean post-10 years of treatment 10-year CVD risk	14.1	14.7	14.7
Averted **QALY loss from CVD events, per 1000 patients treated, compared to JNC8**	1.39	3.01	1.54
Averted **QALY loss from adverse events, per 1000 patients treated, compared to JNC8**	-0.03	-0.09	-0.02
Total QALYs saved, per 1000 patients treated, compared to JNC8	40.0	74.9	44.6

MDPT = Markov Decision Process-based treatment; JNC8 = Eighth Joint National Committee treatment strategy

*"Treated similarly" was defined as rounded mean treatment dose level over the patient's lifetime being the same between the JNC8 and MDPT strategies

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Figure 1. Model schematic

* "High-risk" was defined the same as SPRINT and ACCORD enrollment eligibility criteria except for type 2 diabetes status

Figure 2. Treatment dose levels under each treatment strategy

Figure 3. Mean systolic blood pressure (SBP) levels of individuals achieved under each treatment strategy

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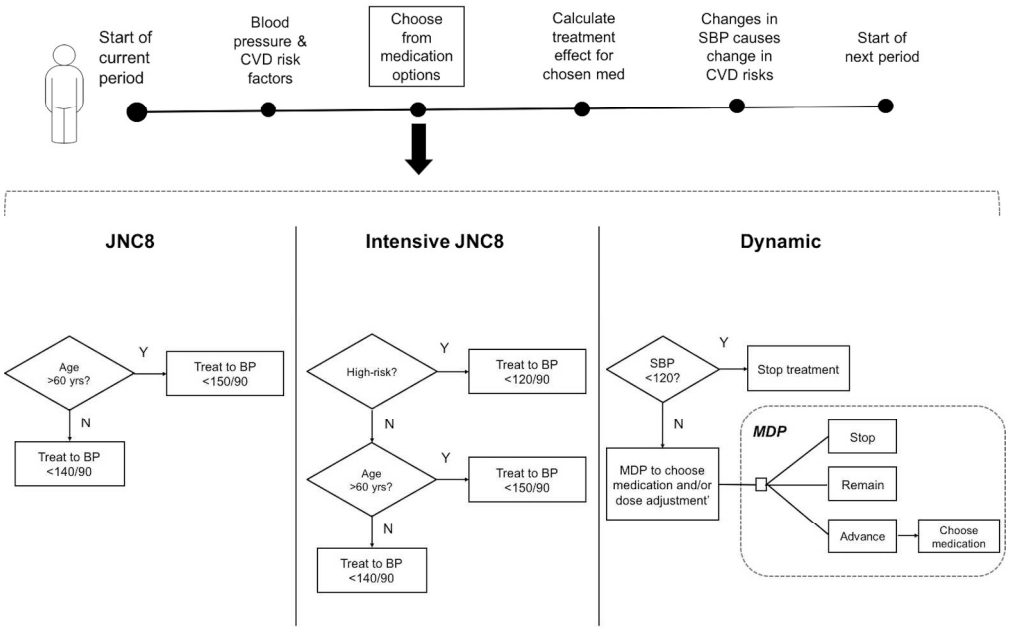

Figure 1. Model schematic

* "High-risk" was defined the same as SPRINT and ACCORD enrollment eligibility criteria except for type 2 diabetes status

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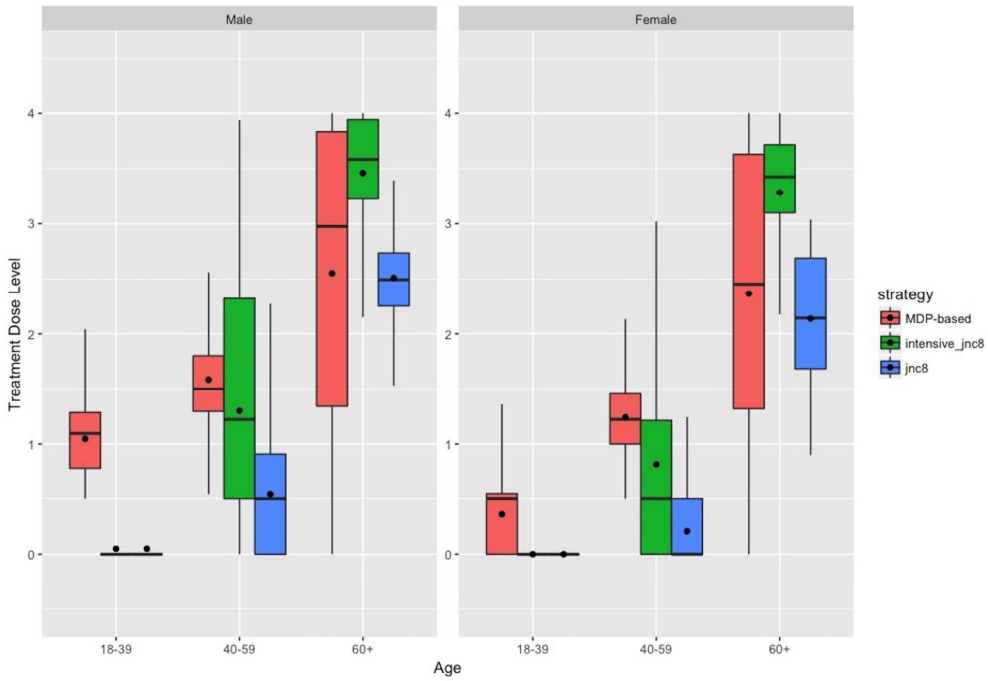

Figure 2. Treatment dose levels under each treatment strategy

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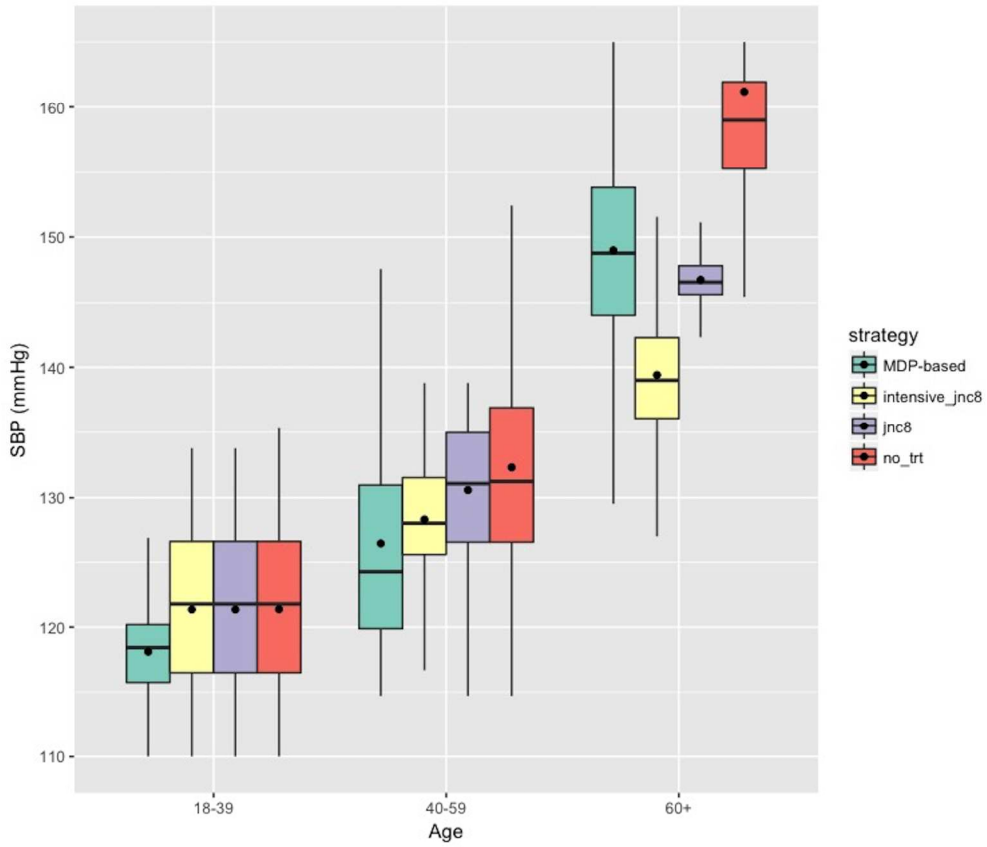

Figure 3. Mean systolic blood pressure (SBP) levels of individuals achieved under each treatment strategy

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PERSONALIZING BLOOD PRESSURE THERAPY: DYNAMIC TREATMENT SELECTION AND MODIFICATION USING A MARKOV DECISION PROCESS MODEL

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eText 1. Model formulation

MDP formulation

Here we present the formulation of the MDP model. The simulation code is available at https://sdr.stanford.edu/. The MDP model is characterized by a state space, action space, transition probabilities, and rewards. A patient may enter one of 7 health states, as illustrated in eFigure 1: (1) Well; (2) Adverse event without CVD history; (3) MI; (4) Stroke; (5) Post CVD; (6) Adverse event with CVD history; (7) Death. Model notation is shown below. The action space consisted of a finite set of possible actions (treatment decisions). A patient could stop a medication treatment, remain on the current medication treatment(s) and dose level(s), or change medication treatment (by increasing a dosage of a current medication, and/or changing the medication). We did not include decreases in dosage in our action space to mimic how current clinical practice (including the protocol in randomized trials) is conducted. Usually blood pressure medication is prescribed, with increases in dosage if necessary, until the patient's blood pressure meets the target blood pressure goal. Once the target blood pressure is reached, the patient no longer changes medication dosage and typically stays on the same dosage for life. The objective of the MDP is to determine the optimal treatment strategy π^* for a single patient that maximizes the patient's expected discounted quality-adjusted life years (QALYs) over a simulated time horizon. The MDP chooses an action to maximize the expected gains by calculating transition probabilities and rewards (discounted QALYs) associated with each action as illustrated in eFigure 2.

Treatment effectiveness was modeled to be mediated through systolic blood pressure (SBP) reduction based on a meta-analysis of 147 randomized clinical trials, in which SBP reduction from treatment was found to be a function of the number of prescribed drugs and the

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dosage level of the drugs.[1] The treatment dose scale and medications used in our model were based on that meta-analysis.[1] In our model, patients can take up to 4 different medications from among the following: angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), beta-blocker, calcium channel Blocker (CCB), and thiazide diuretic. The treatment dose scale is as follows:

0 – No treatment
0.5 – One drug, ½ dose
1 – One drug, 1 dose
1.5 – Two drugs, ½ doses
2 – Two drugs, 1 dose each
2.5 – Three drugs, ½ doses
3 – Three drugs, 1 dose each
3.5 – Four drugs, ½ doses
4 – Four drugs, 1 dose each

Transition probabilities $P_a(s, s')$, are functions of: the patient's post-treatment CVD risk, $r_a(s)$ → $r_a(s) = RR(s)*r(s)$; the likelihood of death from a CVD event, $\rho(s)$; the likelihood of non-CVD death, $\varphi(s)$; the likelihood of side effects from treatment, $\beta_{a,m}(s)$.

The transition probabilities $P_a(s, s')$ are updated in every time step (i.e., every month). At each time step, individuals are faced with either continuing with the current treatment option or advancing to the next level. When transitioning from s to s' state, rewards are given by:

$$R_a(s, s') = Q_a(s, s')$$

At each time step, π will contain the solution and $V(s)$ will contain the discounted sum of the rewards to be earned (on average) by following that solution from state s. The Bellman value function gives the maximized expected QALYs when in state s:

$$V(s) = \sum_{s'} P_a(s, s')(R_a(s, s') + \lambda V(s'))$$

The optimal policy maximizes the sum of expected QALYs over the time horizon:

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$$\pi^*(s) = argmax_a\{\sum_{s'} P_a(s,s')(R_a(s,s') + \lambda V(s'))\}.$$

MDP Model Notation

Variable	Description
t	Time index; t = 0,1,…,T
$d \in D$	Treatment dose options A. A=(1,…,9)
$m \in M$	Number of treatment drugs M. M=(1,…,4)
$b_{min} \in R+$	Minimum allowable SBP
$g \in G$	Multidimensional state of the patient represented by the number of remaining decision epochs in the planning horizon, risk factors including demographic information for the patient (e.g. age, sex, smoking status), and CVD competing risk factors (pretreatment SBP, DBP, total cholesterol, HDL cholesterol, smoking status, hypertension treatment status, diabetes status, CVD history) n = 0,..., N, the number of remaining decision epochs p represents patient demographic information (age, sex, race, income) $b \in$ R+ denotes the pretreatment SBP c represents patient CVD competing risk factors. $s \in$ [1, …,7] denotes the patient health state g = (n; p; b; c; s)
$RR(s) \in [0,1]$	Relative-risk factor when in state s
$r(s) \in [0, 1]$	Patient's pretreatment risk of a CVD event in state s
$r_a(s) \in [0, 1]$	Patient's post treatment risk of a CVD event in state s with action a; $D(s)$*$r(s)$
$P_a(s,s')$	Transition probabilities from state s to s'
$\varphi(s) \in [0, 1]$	Probability of death from non-CVD cause given the patient's post-treatment CVD risk when in state s
$\rho(s) \in [0, 1]$	Probability of death from a CVD event when in state s, given that the patient had a CVD event
$\beta_{a,m}(s) \in [0, 1]$	Probability of experiencing side effects (adverse events) in state s
$Q_a(s,s')$	QALYs associated with transition from s to s'
λ	Discount rate for costs and health benefits

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Microsimulation model formulation

We developed a microsimulation model at the level of the individual. The model is stochastic: we sample from probability distributions of input parameters to generate a distribution of outcomes. The model is run in discrete time steps over the life course of individuals from 2017. Key parameters and data sources are summarized in eTables 4-12.

We classified the synthetic population in this model by combinations of a few key demographic characteristics: age (18-39, 40-59, 60-85 years old), sex, and race/ethnicity (NHANES categories of non-Hispanic white, non-Hispanic black, Mexican-American or other). Because NHANES comprises repeated cross-sectional data, we had to construct a synthetic population to account for the survey weights. We generated 10,000 individuals, following pretreatment guidelines, for each cohort defined by the combinations of these characteristics. We re-ran the model 10,000 times while repeatedly Monte Carlo sampling from the probability distributions of all input parameters to capture uncertainties in our estimates.[2]

Baseline CVD risk factors and prevalent disease cases were assigned to each simulated individual by repeated Monte Carlo sampling from the probability distributions of each of these variables in NHANES, specific to each demographic group. The joint probability distributions of these risk factors were accounted for using multivariate sampling with copula functions, which allows us to capture how these factors are co-dependent. This procedure takes into account the correlation between risk factors. To account for individuals aging, we tracked the age of each simulated individual over the simulation period, and updated each individual's health metrics to account for age-specific health risks by preserving the individual's rank in the population distribution to account for the stability of risk over time and differential survival probability.

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eText 2. Effects of hypertension medication on blood pressure and CVD risks

We estimated the effect of blood pressure medications on lowering blood pressure as a function of dose based on a meta-analysis of 147 randomized placebo controlled trials of blood pressure-lowering drugs in fixed dose,[3] which showed that the five main classes of blood pressure-lowering drugs produce similar reductions in blood pressure. In our model, patients were allowed to take only up to full doses of 4 different medicines, given current data suggesting that increasing blood pressure medications beyond 4 full doses has been found to increase side-effects/adverse effects without providing any incremental benefit for patients.[4] In the JNC8 and Intensive JNC8 strategies, even if the patients' blood pressure levels do not meet the target blood pressure goals, they were not allowed to receive more than 4 full doses of medications. In the MDP-based treatment (MDPT) strategy, patients did not have an option to increase doses if they were receiving 4 full doses.

The blood pressure-lowering effect of the drugs was estimated as a function of treatment dose and pre-treatment blood pressure, and was not dependent on types of drugs, except for beta-blockers. Beta-blockers have been shown to be more effective than the other studied antihypertensive drugs in lowering blood pressure among patients with previous history of CVD (relative risk of 0.71, 95% confidence interval 0.66 to 0.78).[1] We included this effect in our model and found that for patients with CVD history the MDPT tended to favor beta-blockers over other types of drugs.

The estimated effect of one drug at standard dose in lowering blood pressure from a pre-treatment blood pressure P was calculated as $(9.1+0.10(P-154))$ systolic blood pressure. The estimated blood pressure reduction for a higher standard dose was calculated by applying this equation to each drug in turn, allowing for the effect of the first in lowering pre-treatment blood

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pressure for the second, and the second for the third, and so on. The blood pressure reductions from half standard doses were calculated as (R+n*0.078(P−150)) systolic blood pressure, where R is the blood pressure reduction at 150 mm Hg systolic blood pressure, n is the number of drugs, and P is the pretreatment blood pressure. Using these equations yields the following estimates of R:

Number of drugs at standard dose	***R***
One drug half standard dose	6.7
Two drugs half standard dose	13.3
Three drugs half standard dose	19.9
Four drugs half standard dose	26.5

Given SBP changes from blood pressure medication, the relative risk reduction for MI and stroke was estimated using previously published equations (equations (1) and (2) below).[5] The equations were estimated by fitting curves to data from a meta-analysis of prospective patient-level data on blood pressure and CVD mortality.[6]

Slope MI = -1.1009E-05 age^2 + 8.6305 E -04 age + 3.5176 E -02 (1)
Relative risk of MI = 2^(change in SBP*slope MI)

Slope stroke = -2.5946E -05 age^2 + 2.3052E -03 age + 2.2168E -02 (2)
Relative risk of stroke = 2^(change in SBP*slope stroke)

eText 3. Risk of myocardial infarction (MI) or stroke

We used validated equations of monthly risks of MI and stroke estimated by fitting exponential curves to data on age- and sex-specific incidence of first MI and stroke from the Framingham Heart Study (1980-2003), published by the National Heart, Lung, and Blood Institute.[5, 7]

Given no history of MI (x = age in years), monthly risk of MI is:

Male: $y = 0.0001 * e^{0.0312x}$ (3)
Female: $y = 8E - 06 * e^{0.0599x}$ (4)

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Given no history of stroke (x = age in years), monthly risk of stroke is:

$$\text{Male: } y = 9E-06 * e^{0.0622x} \quad (5)$$
$$\text{Female: } y = 3E-06 * e^{0.0741x} \quad (6)$$

Given history of CVD, the risk of MI or stroke without a history of CVD was multiplied by a constant with a mean of 2, standard deviation 1.0204, gamma distribution (shape=3.84166, scale=0.520608).

To account for other CVD risk factors, we adopted a previously published approach in which weights are assigned to each individual based on the following risk factors used in the Framingham risk equations[8, 9]: age, total cholesterol, HDL cholesterol, hypertension treatment status, smoking, and diabetes. Individual Framingham risks were divided by the mean Framingham risk of each cohort (defined by age, sex, race, and income), then used to weight each individual's baseline MI and stroke risk equations, equations (3)-(6). The Framingham risk equations are as follows:

For males:

Individual_FHS_risk = (1-0.88936)*exp((3.06117*log(age)+1.12370*log(total_cholesterol)-0.93263*log(HDL_cholesterol)+1.99881*log(SBP_treated)+1.93303*log(SBP_untreated)+0.65451*smoking+0.57367*diabetes)- 23.9802)

For females:

Individual_FHS_risk = (1-0.95012)*exp((2.32888*log(age)+1.20904*log(total_cholesterol)-0.70833*log(HDL_cholesterol)+2.82263*log(SBP_treated)+2.76157*log(SBP_untreated)+0.52873*smoking+0.69154*diabetes)-26.1931)

$$\text{Weights assigned to individual} = \frac{\text{Individual FHS risk}}{\text{Mean FHS risk of each cohort}}$$

eText 4. Mortality after myocardial infarction (MI) or stroke

We used validated equations of age- and sex-specific risk of mortality after MI and stroke developed by fitting exponential curves to the ratio of incidence of fatal events to total incidence

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of events. Data on fatal MI and total incidence of MI was obtained from the Framingham Heart Study. The ratio of fatal stroke to stroke incidence was obtained from the Cardiovascular Health Study.[5, 7] This yields the following estimated mortality risks.

Risk of mortality after MI (x = age in years):

Male: $y = 0.0289 * e^{0.0269x}$

Female: $y = 0.0004 * e^{0.0706x}$

Risk of mortality after stroke (x = age in years):

Male: $y = 0.0003 * e^{0.0782x}$

Female: $y = 0.0034 * e^{0.0428x}$

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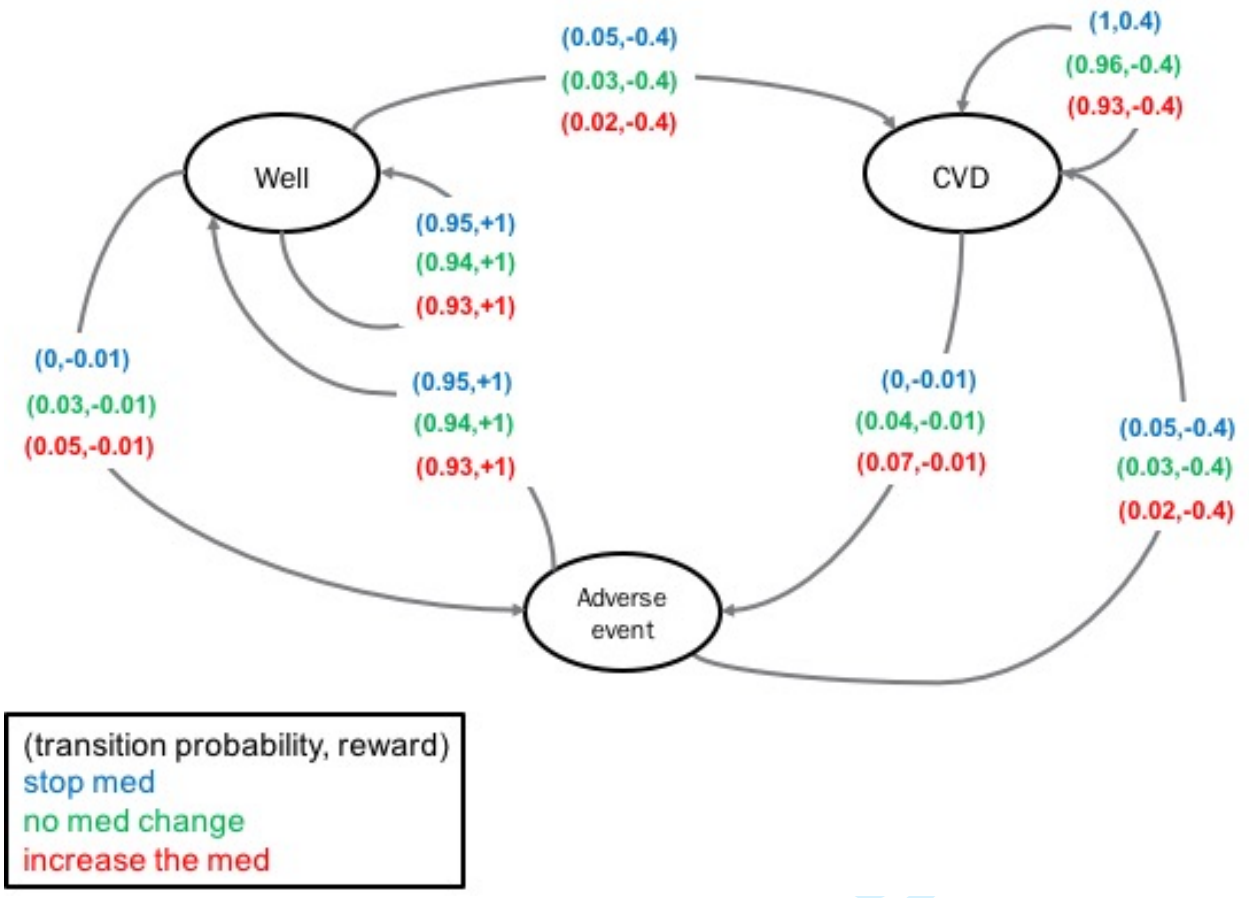
eFigure 1. Illustration of decision making process in Markov Decision Process. This figure illustrates how the MDP chooses the optimal action (treatment decision) at each decision epoch. The transition probabilities from the current state to the next are determined by which action is taken, and each transition is associated with corresponding rewards. This illustration has three actions in different colors. The numbers in each parenthesis are the transition probability and reward associated with each action. The MDP chooses an action that will maximize total rewards by calculating expected rewards from each action over the simulated horizon.



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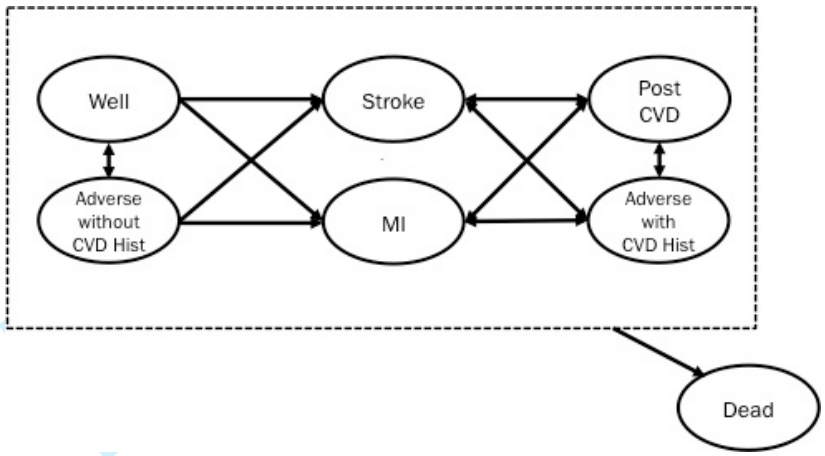
eFigure 2. Schematic of health states in Markov Decision Process



CVD: Cardiovascular disease; CVD Hist: CVD History

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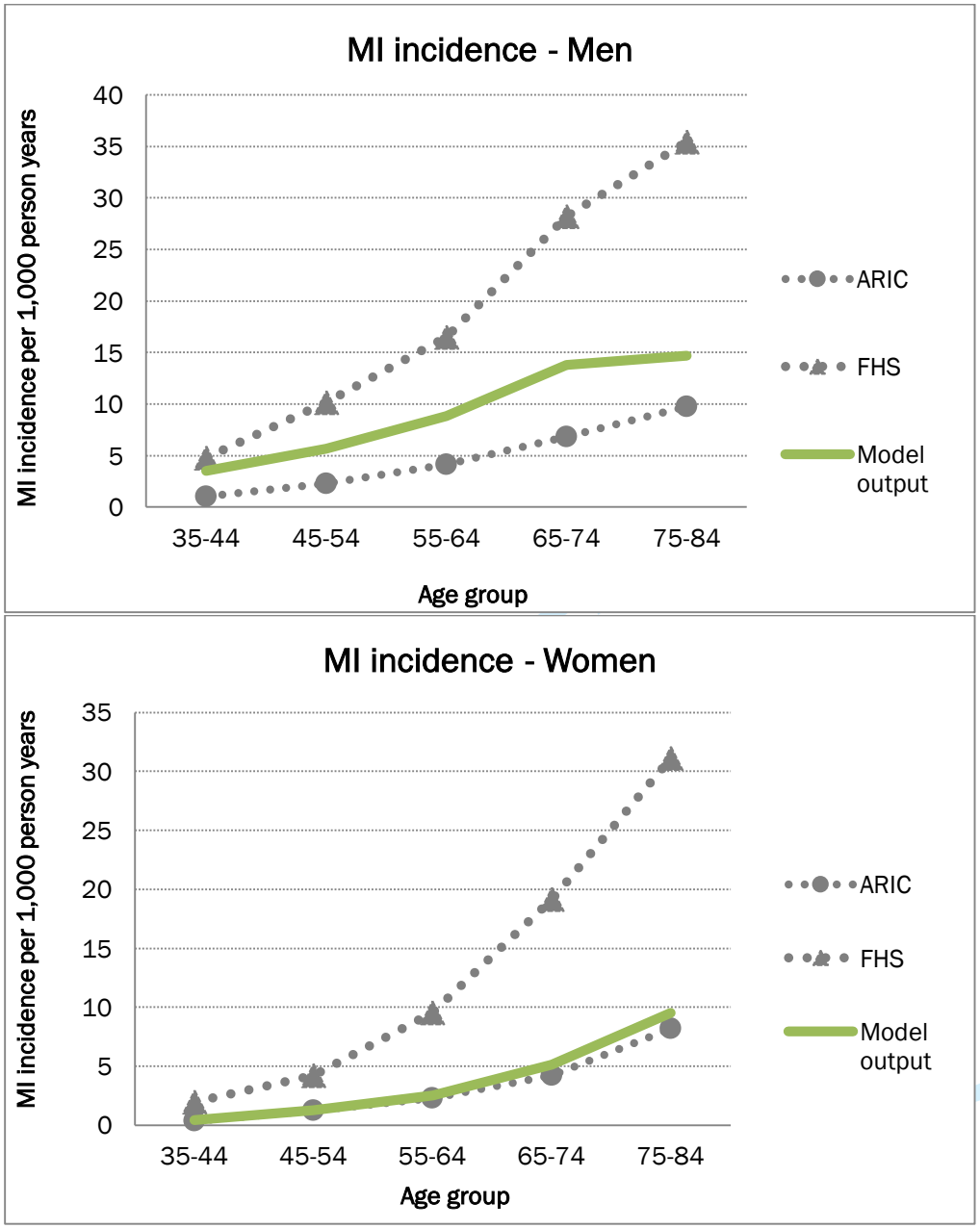
eFigure 3. Calibration results: MI incidence. We considered our targets were met if the projected incidence fell within the interval between the estimates from the Framingham Heart Study (FHS) and the Atherosclerosis Risk in Communities study (ARIC) which are, respectively more-inclusive and less-inclusive measures of composite CVD outcomes.



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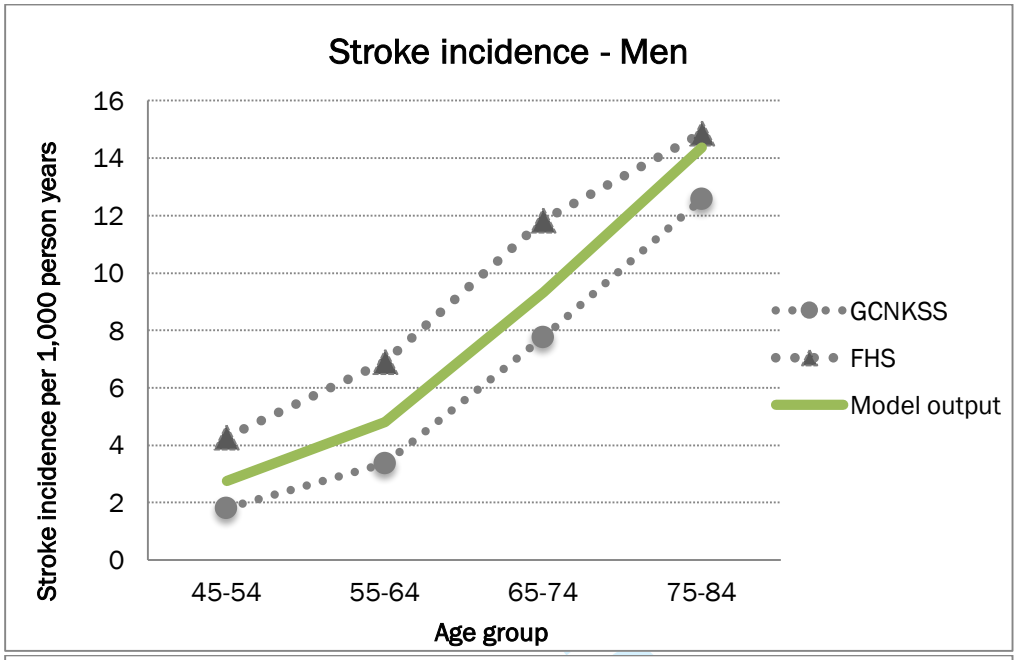
eFigure 4. Calibration results: stroke incidence. We considered our targets were met if the projected incidence fell within the interval between the estimates from Framingham Heart Study (FHS) and the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS)



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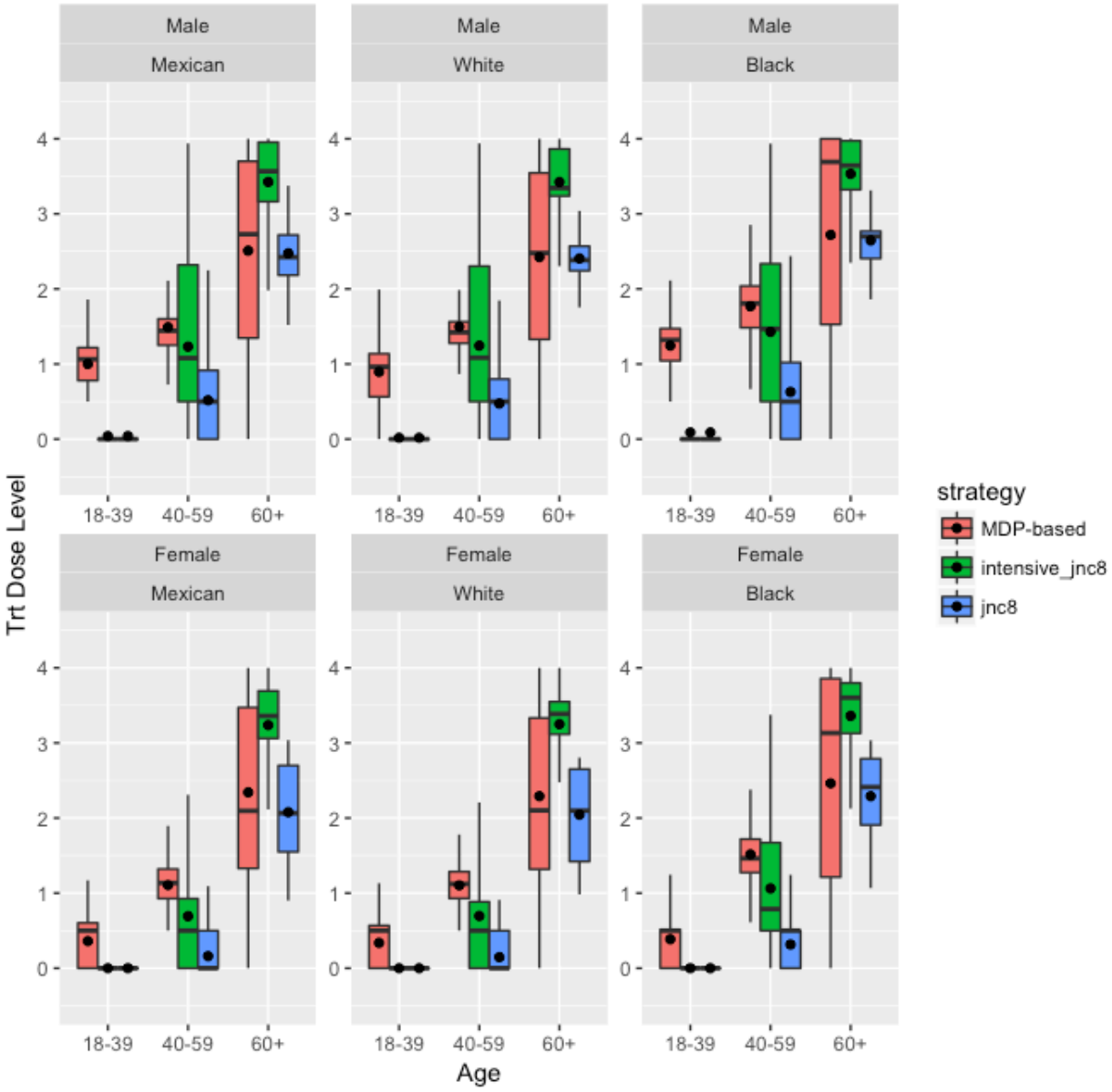
eFigure 5. Treatment dose levels by age, sex, and race under each treatment strategy



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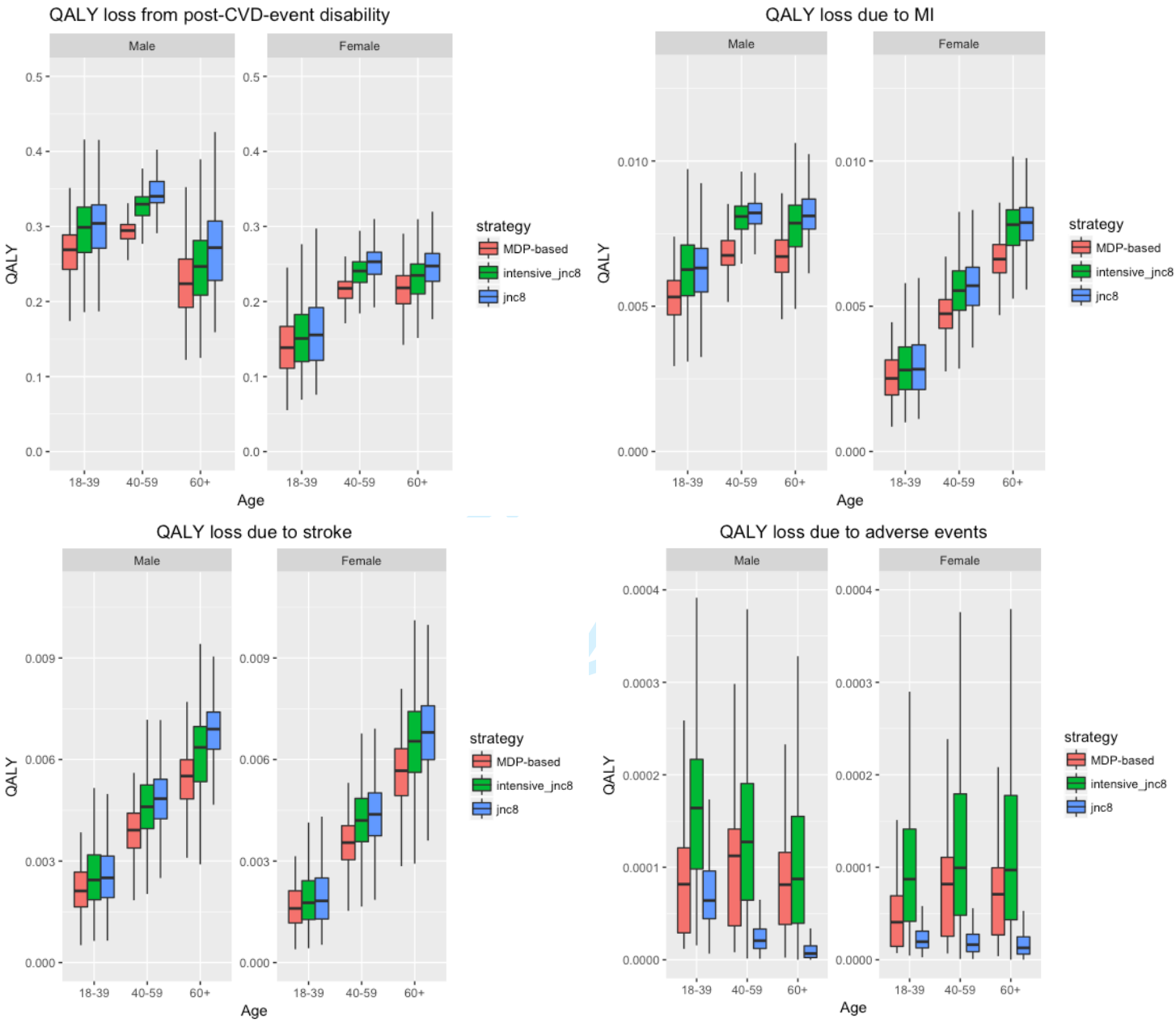
eFigure 6. QALYs in each disease state over patient lifetimes



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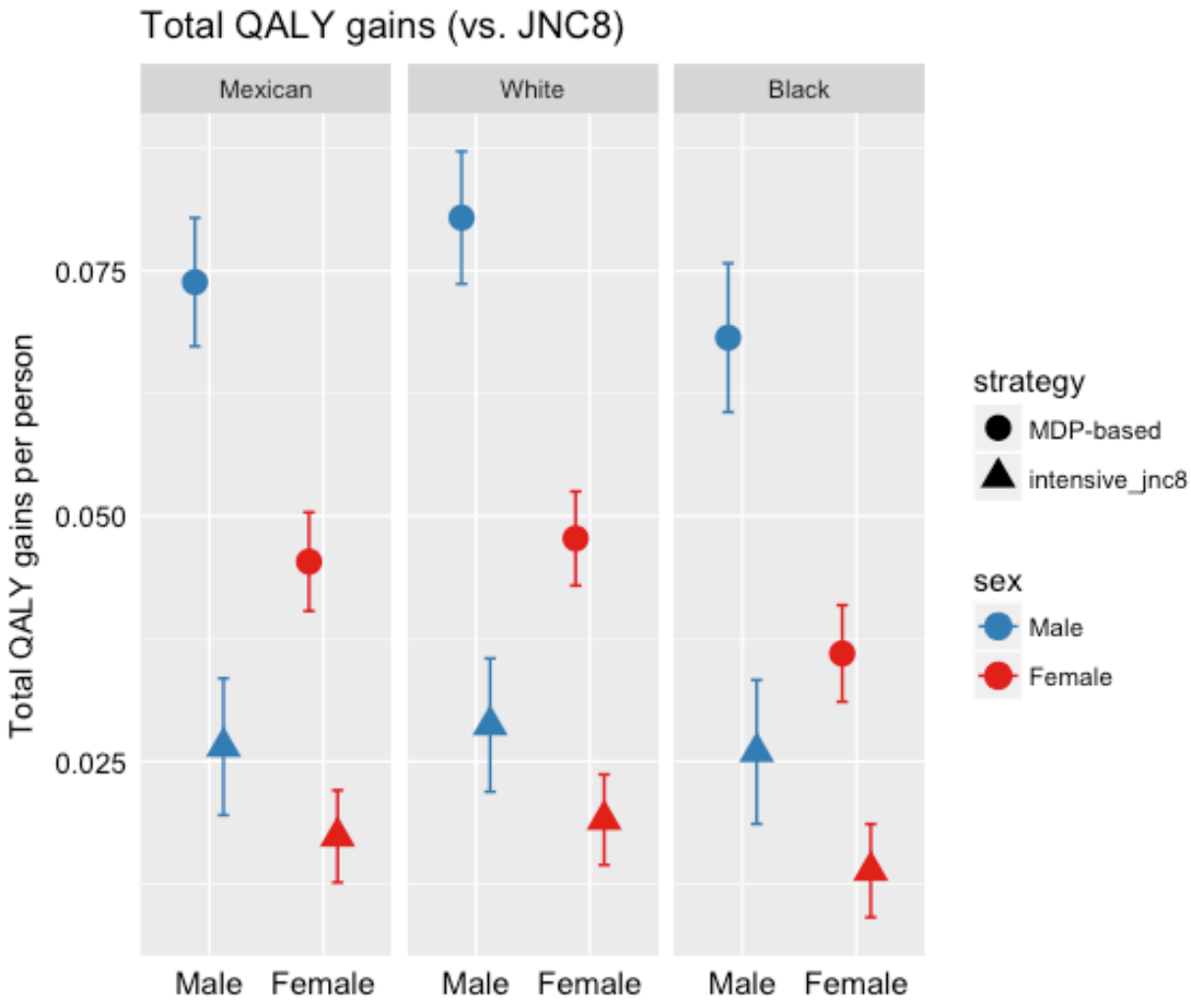
eFigure 7. Total QALY gains over patient lifetimes for the Intensive JNC8 strategy and the MDP-based treatment strategy compared to the JNC8 strategy



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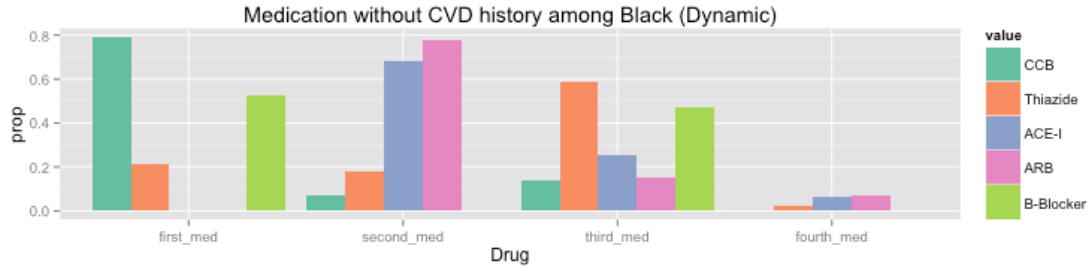
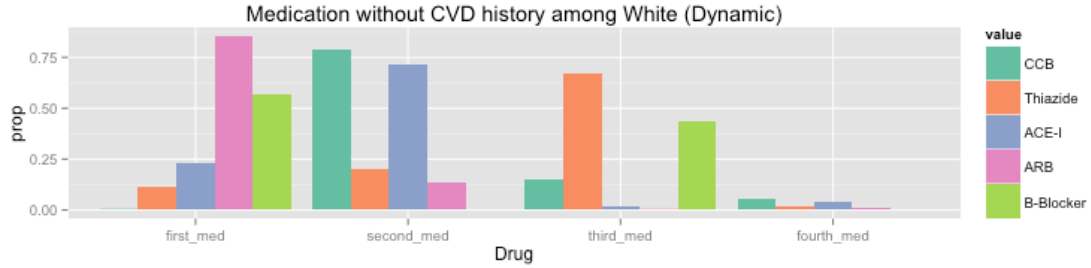
eFigure 8. Comparison of medications selected by MDP-based treatment (MDPT) approach vs. current guidelines

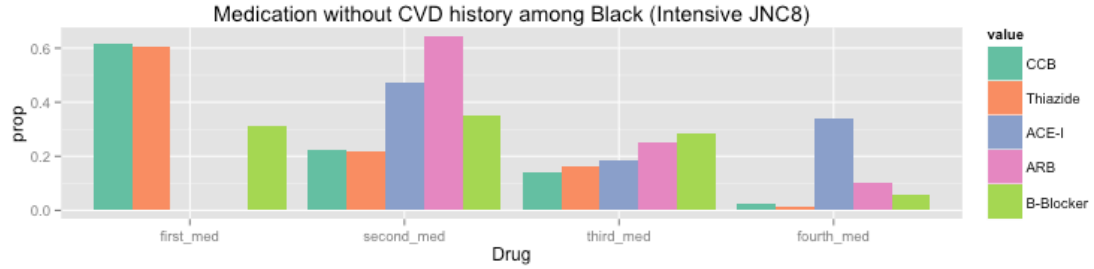
Without CVD History

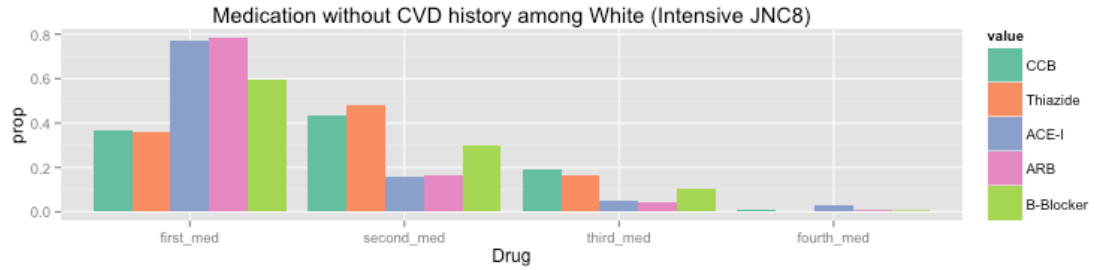
MDPT *(Dynamic: MDP-based treamtent)*





JNC8





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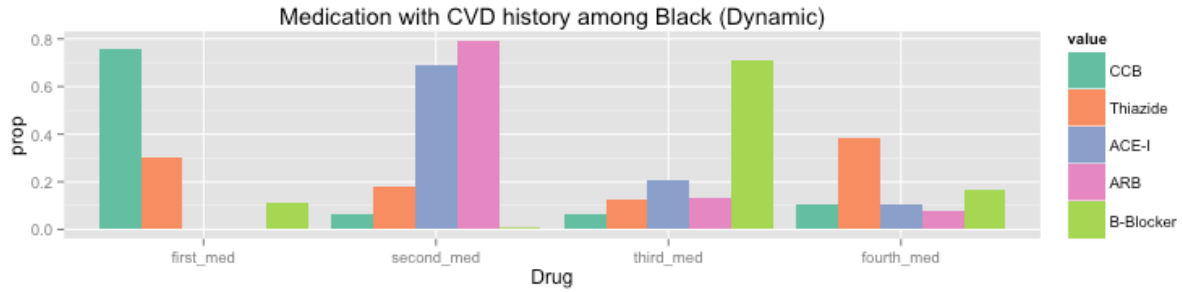
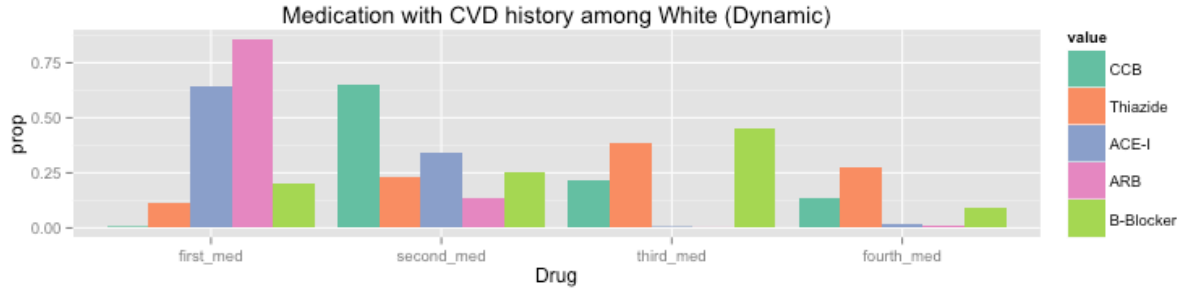
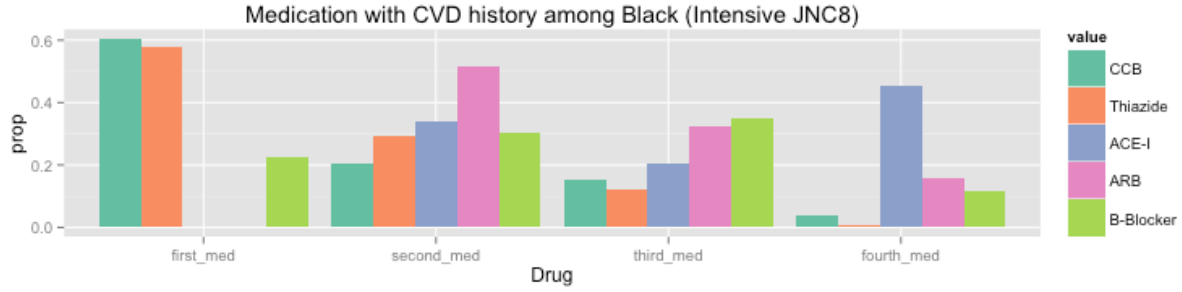
With CVD History

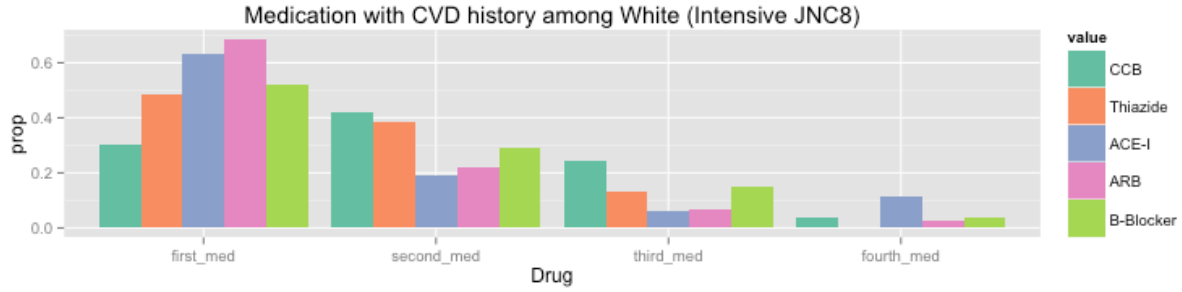
MDPT (Dynamic*: MDP-based treatment)*





JNC8





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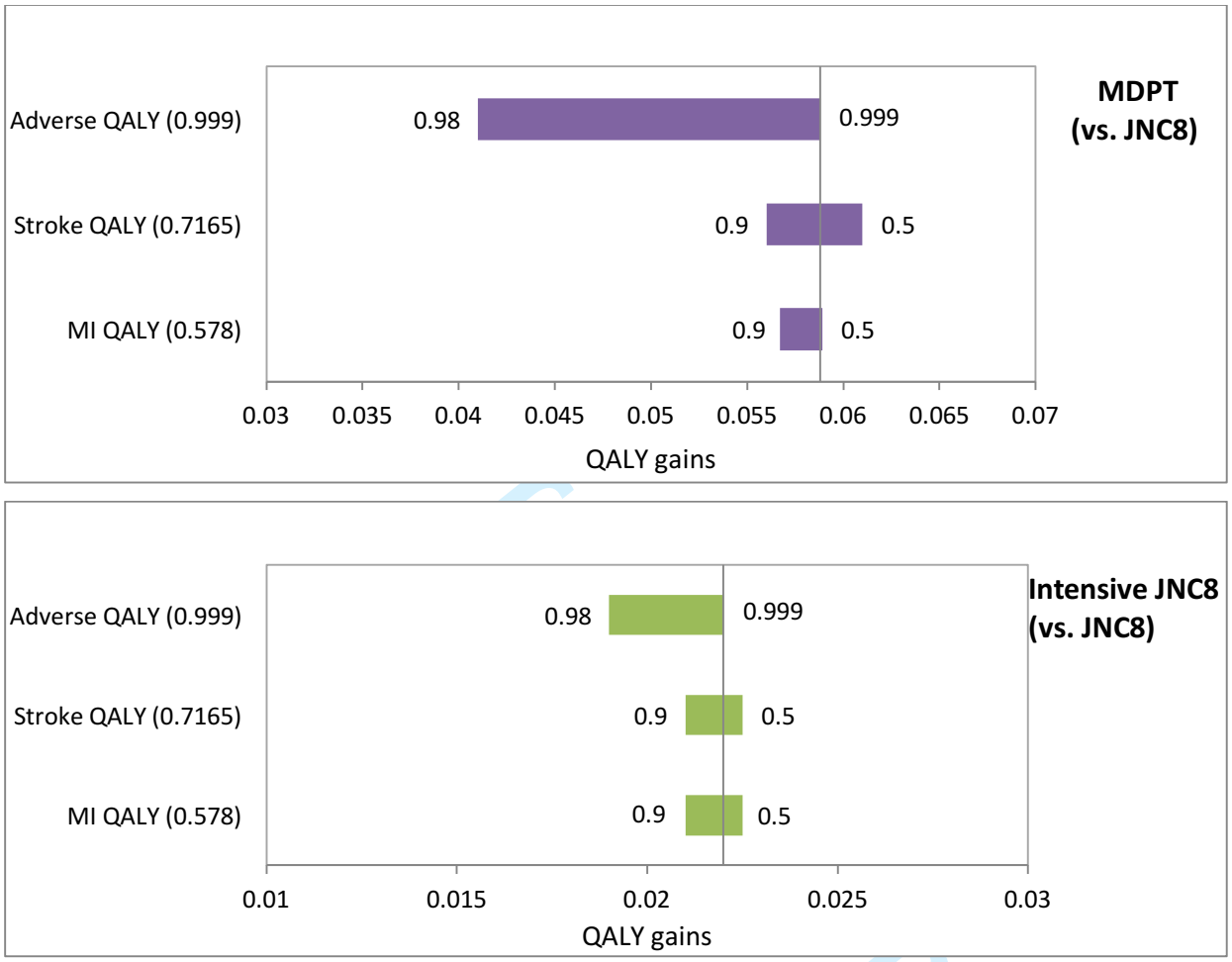
eFigure 9. Sensitivity analysis: QALY gains from the MDP-based treatment (MDPT) strategy and the Intensive JNC8 strategy (vs. JNC8)

The vertical lines represent the QALY gains in the base case analysis, and the horizontal bars represent the variation of the QALY gains given variations of parameters. The numbers at each end of the bars represent the lower and upper bounds of the value used for each parameter.



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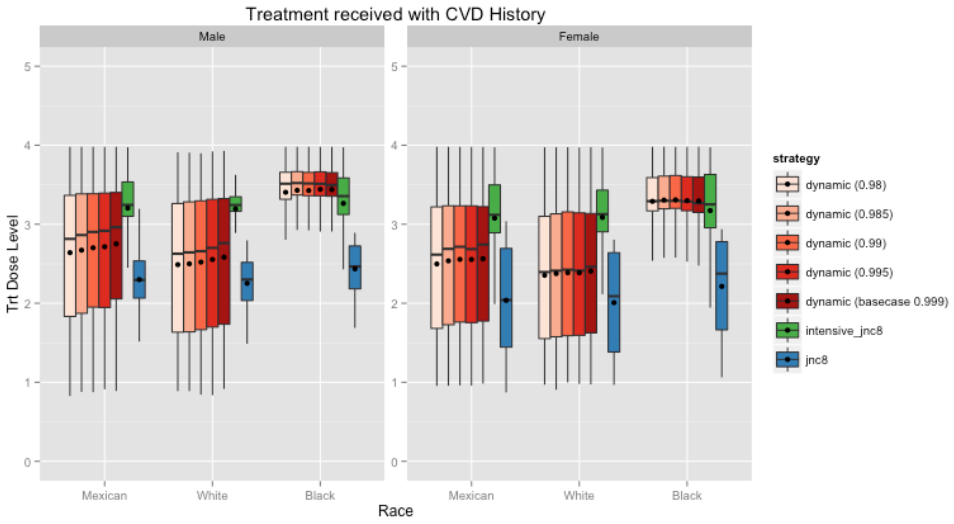
eFigure 10. Sensitivity analyses: Treatment dose levels given variation in QALY weights
Adverse event QALY weights (dynamic: MDP-based)



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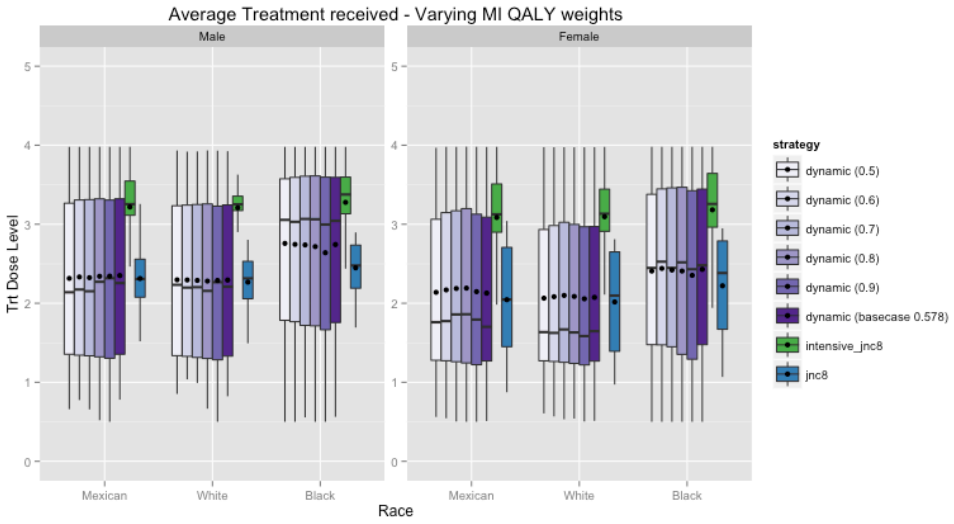
MI QALY weights (dynamic: MDP-based)



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eTable 4. Baseline MI History Prevalence (%)

		Age					
Sex	**Race**	**20-39**	**20-39**	**40-59**	**40-59**	**60-85**	**60-e85**
		Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Male	Mexican	0.00	NA	0.72	0.25	6.92	1.04
	NH White	0.21	0.04	2.31	0.18	15.42	0.48
	NH Black	0.00	NA	4.43	0.61	12.11	0.75
Female	Mexican	0.00	NA	1.26	0.29	4.11	0.60
	NH White	1.34	0.22	1.32	0.16	8.71	0.38
	NH Black	0	NA	0	NA	5.91	0.06

eTable 5. Baseline Stroke History Prevalence (%)

		Age					
Sex	**Race**	**20-39**	**20-39**	**40-59**	**40-59**	**60-85**	**60-e85**
		Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Male	Mexican	0.00	NA	1.91	1.89	9.43	3.94
	NH White	0.14	0.13	0.42	0.24	6.51	1.48
	NH Black	0.00	NA	1.98	1.72	12.61	3.76
Female	Mexican	0.00	NA	1.51	8.66	2.68	2.30
	NH White	1.05	1.04	1.69	0.61	7.95	1.72
	NH Black	0.33	0.32	4.49	2.32	8.02	2.95

eTable 6. Baseline Hypertension Medication Use Prevalence (%)

		Age					
Sex	**Race**	**20-39**	**20-39**	**40-59**	**40-59**	**60-85**	**60-e85**
		Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Male	Mexican	1.46	1.48	9.75	5.26	41.66	8.53
	NH White	3.95	1.49	14.25	2.35	52.41	2.41
	NH Black	5.76	1.41	33.54	4.48	62.41	3.91
Female	Mexican	7.88	5.24	6.47	3.48	47.86	10.54
	NH White	0.81	0.64	24.70	3.30	54.23	3.42
	NH Black	9.48	3.41	43.57	4.95	75.36	6.23

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eTable 7. Baseline Systolic Blood Pressure (mmHg)

		Age					
Sex	**Race**	**20-39**	**20-39**	**40-59**	**40-59**	**60-85**	**60-e85**
		Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Male	Mexican	121.4	1.2	124.1	3.2	135.1	7.6
	NH White	120.5	1.2	124.4	1.2	131.1	1.1
	NH Black	123.5	1.0	128.5	1.4	136.8	1.2
Female	Mexican	110.6	1.4	120.3	2.4	138.5	3.9
	NH White	109.9	0.7	121.2	1.1	135.3	1.3
	NH Black	113.8	1.3	128.5	1.9	140.4	1.9

eTable 8. Baseline Total Cholesterol (mmol/L)

		Age					
Sex	**Race**	**20-39**	**20-39**	**40-59**	**40-59**	**60-85**	**60-e85**
		Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Male	Mexican	179.1	5.4	208.8	6.8	187.8	8.1
	NH White	191.5	4.4	206.4	2.1	187.8	1.4
	NH Black	182.3	3.3	190.8	5.0	184.9	4.6
Female	Mexican	187.2	5.6	208.9	6.7	208.6	9.5
	NH White	189.8	2.9	209.6	2.9	208.5	2.4
	NH Black	182.9	2.8	201.4	3.9	206.9	5.6

eTable 9. Baseline HDL Cholesterol (mmol/L)

		Age					
Sex	**Race**	**20-39**	**20-39**	**40-59**	**40-59**	**60-85**	**60-e85**
		Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Male	Mexican	44.8	1.8	52.8	3.7	48.4	4.4
	NH White	47.3	1.1	49.1	0.8	51.2	0.6
	NH Black	49.5	1.5	54.9	2.7	53.0	0.7
Female	Mexican	58.7	2.4	55.7	4.1	53.3	2.4
	NH White	58.5	1.0	60.0	0.9	63.0	1.0
	NH Black	59.4	1.6	62.4	1.7	64.7	3.2

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eTable10. Baseline Smoking Prevalence (%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-e85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	26.7	6.1	18.4	10.6	16.9	4.3
	NH White	30.9	3.1	24.1	3.6	11.9	2.8
	NH Black	27.6	4.5	35.5	6.8	22.1	5.0
Female	Mexican	9.5	4.5	26.2	9.0	9.9	3.1
	NH White	27.2	4.5	16.4	3.0	12.7	2.5
	NH Black	23.7	6.6	22.7	4.6	15.1	4.5

eTable 11. Baseline Type 2 Diabetes Prevalence (%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-e85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	0	NA	19.4	7.3	37.2	9.3
	NH White	1.3	0.7	4.9	1.3	14.7	2.2
	NH Black	5.1	1.5	14.2	5.7	32.9	5.0
Female	Mexican	2.7	1.2	5.2	2.1	30.7	4.8
	NH White	2.8	1.7	4.3	1.1	12.9	1.6
	NH Black	2.6	1.6	15.8	4.5	34.1	3.8

eTable 12. Baseline Chronic Kidney Disease (CKD) Prevalence (%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-e85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	10.5	3.3	2.6	2.3	19.4	5.9
	NH White	14.5	2.0	17.6	2.1	14.7	2.9
	NH Black	1.4	0.7	4.2	2.1	10.6	3.3
Female	Mexican	25.8	6.9	22.5	6.6	48.5	4.4
	NH White	23.2	4.3	41.1	2.4	42.8	3.2
	NH Black	6.9	1.7	6.8	1.8	13.6	3.4

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BMJ Open

Dynamic Treatment Selection and Modification for Personalized Blood Pressure Therapy using a Markov Decision Process Model: A Cost-effectiveness Analysis

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Primary Subject Heading:	Health services research
Secondary Subject Heading:	Patient-centred medicine, Cardiovascular medicine, Research methods
Keywords:	Hypertension < CARDIOLOGY, Cardiovascular disease, Personalized medicine

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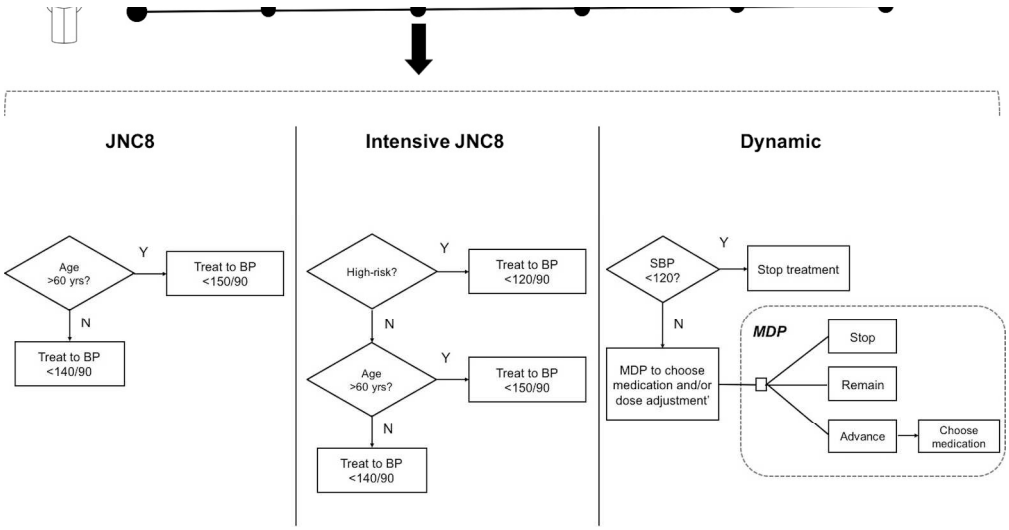

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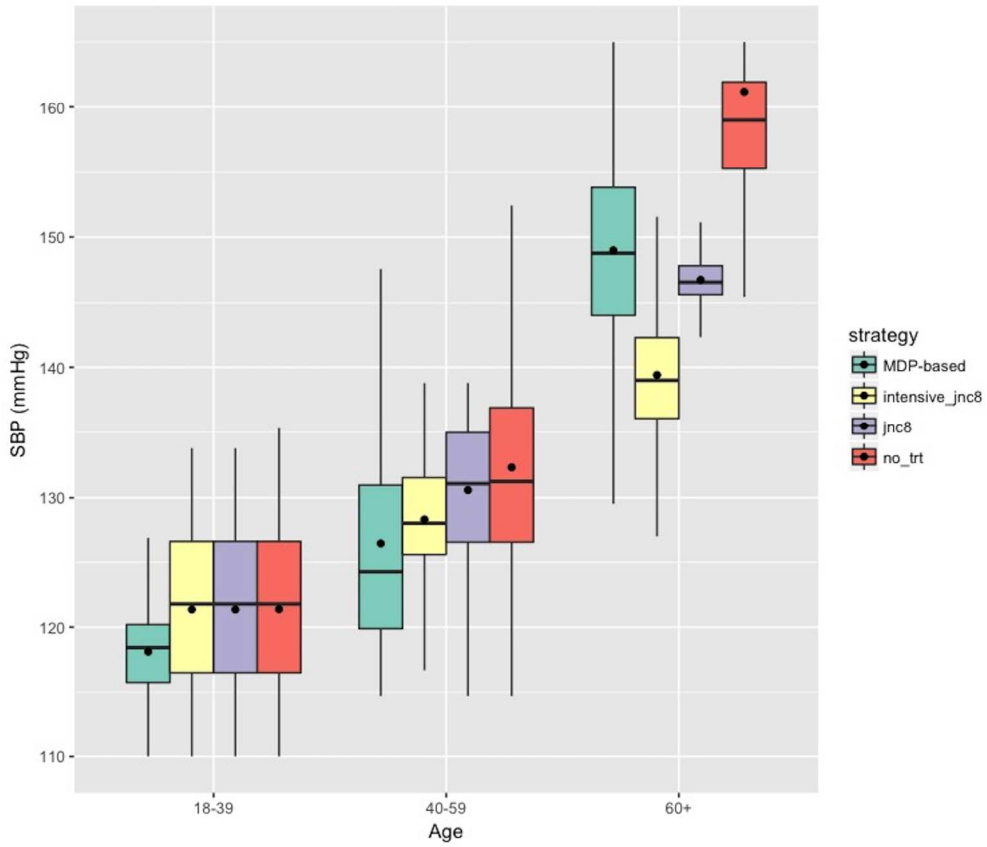

Figure 3. Mean systolic blood pressure (SBP) levels of individuals achieved under each treatment strategy

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eText 1. Model formulation

MDP formulation

Herewe present the formulation of the MDP model. The simulation code is available at https://sdr.stanford.edu/. The MDP model is characterized by a state space, action space, transition probabilities, and rewards. A patient may enter one of 7 health states, as illustrated in eFigure 1: (1) Well; (2) Adverse event without CVD history; (3) MI; (4) Stroke; (5) Post CVD; (6) Adverse event with CVD history; (7) Death. Model notation is shown below. The action space consisted of a finite set of possible actions (treatment decisions). A patient could stop a medication treatment, remain on the current medication treatment(s) and dose level(s), or change medication treatment (by increasing a dosage of a current medication, and/or changing the medication). We did not include decreases in dosage in our action space to mimic how current clinical practice (including the protocol in randomized trials) is conducted. Usually blood pressure medication is prescribed, with increases in dosage if necessary, until the patientÕs blood pressure meets the target blood pressure goal. Once the target blood pressure is reached, the patient no longer changes medication dosage and typically stays on the same dosage for life. The objective of the MDP is to determine the optimal treatment strategy for a single patient that maximizes the patientÕs expected discounted quality-adjusted life years (QALYs) over a simulated time horizon. The MDP chooses an action to maximize the expected gains by calculating transition probabilities and rewards (discounted QALYs) associated with each action as illustrated in eFigure 2.

Treatment effectiveness was modeled to be mediated through systolic blood pressure (SBP) reduction based on a meta-analysis of 147 randomized clinical trials, in which SBP reduction from treatment was found to be a function of the number of prescribed drugs and the

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dosage level of the drugs.[1] The treatment dose scale and medications used in our model were based on that meta-analysis.[1] In our model, patients can take up to 4 different medications from among the following: angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), beta-blocker, calcium channel Blocker (CCB), and thiazide diuretic. The treatment dose scale is as follows:

0 – No treatment
0.5 – One drug, ½ dose
1 – One drug, 1 dose
1.5 – Two drugs, ½ doses
2 – Two drugs, 1 dose each
2.5 – Three drugs, ½ doses
3 – Three drugs, 1 dose each
3.5 – Four drugs, ½ doses
4 – Four drugs, 1 dose each

Transition probabilities, $P_a(s, s')$, are functions of the patient's post-treatment CVD risk, $r_a(s)$ → $r_a(s) = RR(s) * r(s)$; the likelihood of death from a CVD event, $\rho(s)$; the likelihood of non-CVD death, $\varphi(s)$; the likelihood of side effects from treatment, $\beta_{a,m}(s)$.

The transition probabilities $P_a(s, s')$ are updated in every time step (i.e., every month). At each time step, individuals are faced with either continuing with the current treatment option or advancing to the next level. When transitioning from s to s' state, rewards are given by:

$$R_a(s, s') = Q_a(s, s')$$

At each time step, π will contain the solution and $V(s)$ will contain the discounted sum of the rewards to be earned (on average) by following that solution from state s. The Bellman value function gives the maximized expected QALYs when in state s:

$$V(s) = \sum_{s'} P_a(s, s')(R_a(s, s') + \lambda V(s'))$$

The optimal policy maximizes the sum of expected QALYs over the time horizon:

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$$\pi^*(s) = argmax_a\{\sum_{s'} P_a(s,s')(R_a(s,s') + \lambda V(s'))\}.$$

MDP Model Notation

Variable	Description
t	Time index; t = 0,1,É, T
$d \in D$	Treatment dose options A=(1,É ,9)
$m \in M$	Number of treatment drugs M. M=(1,É,4)
$b_{min} \in R+$	Minimum allowable SBP
$g \in G$	Multidimensional state of the patient represented by the number of remaining decision epochs in the planning horizon, risk factors including demographic information for the patient (e.g. age, sex, smoking status), CVD competing risk factors (pretreatment SBP, DBP, total cholesterol, HDL cholesterol, smoking status, hypertension treatment status, diabetes status, CVD history) n = 0,…, N, the number of remaining decision epochs p represents patient demographic information (age, sex, race, income) $b \in$ R+ denotes the pretreatment SBP c represents patient CVD competing risk factors. $s \in$ [1, É,7] denotes the patient health state g = (n; p; b; c; s)
$RR(s) \in$ [0,1]	Relative risk factor when in state s
$r(s) \in$ [0, 1]	Patient's pretreatment risk of a CVD event in state s
$r_a(s) \in$ [0, 1]	PatientÕs post treatment risk of a CVD event in state s with action a; $D(s)*r(s)$
$P_a(s,s')$	Transition probabilities from state s to s'
$\varphi(s) \in$ [0, 1]	Probability of death from non-CVD cause given the patientÕs post-treatment CVD risk when in state s
$\rho(s) \in$ [0, 1]	Probability of death from a CVD event when in state s, given that the patient had a CVD event
$\beta_{a,m}(s) \in$ [0, 1]	Probability of experiencing side effects (adverse events) in s state
$Q_a(s,s')$	QALYs associated with transition from s to s'
λ	Discount rate for costs and health benefits

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Microsimulation model formulation

We developed a microsimulation model at the level of the individual. The model is stochastic; we sample from probability distributions of input parameters to generate a distribution of outcomes. The model is run in discrete time steps over the course of individuals' lives from 2017. Key parameters and data sources are summarized in eTables 1-3.

We classified the synthetic population in this model by combinations of a few key demographic characteristics: age (18-39, 40-59, 60-85 years old), sex, and race/ethnicity (NHANES categories of non-Hispanic white, non-Hispanic black, Mexican American or other). Because NHANES comprises repeated cross-sectional data, we had to construct a synthetic population to account for the survey weights. We generated 10,000 individuals, following pretreatment guidelines, for each cohort defined by the combinations of these characteristics. We re-ran the model 10,000 times while repeatedly Monte Carlo sampling from the probability distributions of all input parameters to capture uncertainties in our estimates.[2] Baseline characteristics between the simulated population and NHANES participants were compared using chi-squared tests and t-tests (eTable 2).

Baseline CVD risk factors and prevalent disease cases were assigned to each simulated individual by repeated Monte Carlo sampling from the probability distributions of each of these variables in NHANES, specific to each demographic group. The joint probability distributions of these risk factors were accounted for using multivariate sampling with copula functions, which allows us to capture how these factors are dependent. This procedure takes into account the correlation between risk factors. To account for individuals aging, we tracked the age of each simulated individual over the simulation period, and updated each individual's health metrics to account for age-specific health risks by preserving the individual's rank in the population

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distribution to account for the stability of risk over time and differential survival probability.

eText 2. Effects ofhypertension medicationon blood pressure and CVDrisks

We estimated the effect of blood pressure medications on lowering blood pressure as a function of dose based on a meta-analysis of 147 randomized placebo controlled trials of blood pressure-lowering drugs in fixed dose,[3] which showed that the five main classes of blood pressure-lowering drugs produce similar reductions in blood pressure. In our model, patients were allowed to take only up to full doses of 4 different medicines, given current data suggesting that increasing blood pressure medications beyond 4 full doses has been found to increase side effects/adverse effects without providing any incremental benefit for patients.[4] In the JNC8 and Intensive JNC8 strategies, even if the patientsÕ blood pressure levels do not meet the target blood pressure goals, they were not allowed to receive more than 4 full doses of medications. In the MDP-based treatment (MDPT) strategy, patients did not have an option to increase doses if they were receiving 4 full doses.

The blood pressure-lowering effect of the drugs was estimated as a function of treatment dose and pre-treatment blood pressure, and was not dependent on types of drugs, except for beta blockers. Beta-blockers have been shown to be more effective than the other studied antihypertensive drugs in lowering blood pressure among patients with previous history of CVD (relative risk of 0.71, 95% confidence interval 0.66 to 0.78).[1] We included this effect in our model and found that for patients with CVD history, the MDPT tended to favor beta-blockers over other types of drugs.

The estimated effect of one drug at standard dose in lowering blood pressure from pre-treatment blood pressure P was calculated as $(9.1+0.10(P-154))$ systolic blood pressure. The estimated blood pressure reduction for higher standard dose was calculated by applying this

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equation to each drug in turn, allowing for the effect of the first in lowering pretreatment blood pressure for the second, and the second for the third, and so on. The blood pressure reductions from half standard dose were calculated as $(R + n * 0.078(P - 150))$ systolic blood pressure, where R is the blood pressure reduction at 150 mm Hg systolic blood pressure, n is the number of drugs, and P is the pretreatment blood pressure. Using these equations yields the following estimates of R:

Number of drugs at standard dose	R
One drug half standard dose	6.7
Two drugs half standard dose	13.3
Three drugs half standard dose	19.9
Four drugs half standard dose	26.5

Given SBP changes from blood pressure medication, the relative risk reduction for MI and stroke was estimated using previously published equations (equations (1) and (2) below).[5] The equations were estimated by fitting curves to data from a meta-analysis of prospective patient level data on blood pressure and CVD mortality.[6]

$$\text{Slope MI} = -1.1009E\text{-}05 \times \text{age}^2 + 8.6305E\text{-}04 \times \text{age} + 3.5176E\text{-}02 \quad (1)$$
$$\text{Relative risk of MI} = 2^{(\text{change in SBP} * \text{slope MI})}$$

$$\text{Slope stroke} = 2.5946E\text{-}05 \times \text{age}^2 + 2.3052E\text{-}03 \times \text{age} + 2.2168E\text{-}02 \quad (2)$$
$$\text{Relative risk of stroke} = 2^{(\text{change in SBP} * \text{slope stroke})}$$

eText 3. Risk of myocardial infarction (MI) or stroke

We used validated equations of monthly risks of MI and stroke estimated by fitting exponential curves to data on age- and sex-specific incidence of first MI and stroke from the Framingham Heart Study (1982-2003), published by the National Heart, Lung, and Blood Institute.[5, 7]

Given no history of MI (x = age in years), monthly risk of MI is:

$$\text{Male: } y = 0.0001 * e^{0.0312x} \quad (3)$$
$$\text{Female: } y = 8E - 06 * e^{0.0599x} \quad (4)$$

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Given no history of stroke (x = age in years), monthly risk of stroke is:

$$\text{Male: } y = 9E-06 * e^{0.0622x} \quad (5)$$

$$\text{Female: } y = 3E-06 * e^{0.0741x} \quad (6)$$

Given history of CVD, the risk of MI or stroke without a history of CVD was multiplied by a constant with a mean of 2, standard deviation 1.0204, gamma distribution (shape=3.84166, scale=0.520608).

To account for other CVD risk factors, we adopted a previously published approach[8,9] in which weights are assigned to each individual based on the following risk factors used in the Framingham risk equations: age, total cholesterol, HDL cholesterol, hypertension treatment status, smoking, and diabetes. Individual Framingham risks were divided by the mean Framingham risk of each cohort (defined by age, sex, race, and income), and used to weight each individual's baseline MI and stroke risk equations (equations (3)-(6)). The Framingham risk equations are as follows:

For males:

Individual_FHS_risk = (1-0.88936)*exp((3.06117*log(age) + 1.12370*log(total_cholesterol) + 0.93263*log(HDL_cholesterol) + 1.99881*log(SBP_treated) + 1.93303*log(SBP_untreated) + 0.65451*smoking + 0.57367*diabetes - 23.9802)

For females:

Individual_FHS_risk = (1-0.95012)*exp((2.32888*log(age) + 1.20904*log(total_cholesterol) - 0.70833*log(HDL_cholesterol) + 2.82263*log(SBP_treated) + 2.76157*log(SBP_untreated) + 0.52873*smoking + 0.69154*diabetes - 26.1931)

$$\text{Weights assigned to individual} = \frac{\text{Individual FHS risk}}{\text{Mean FHS risk of each cohort}}$$

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eText 4. Mortality after myocardial infarction (MI) or stroke

We used validated equations of age- and sex-specific risk of mortality after MI and stroke developed by fitting exponential curves to the ratio of incident fatal events to total incidence of events. Data on fatal MI and total incidence of MI was obtained from the Framingham Heart Study. The ratio of fatal stroke to stroke incidence was obtained from the Cardiovascular Health Study.[5, 7] This yields the following estimated mortality risks.

Risk of mortality after MI (x = age in years):

Male: $y = 0.0289 * e^{0.0269x}$

Female: $y = 0.0004 * e^{0.0706x}$

Risk of mortality after stroke (x = age in years):

Male: $y = 0.0003 * e^{0.0782x}$

Female: $y = 0.0034 * e^{0.0428x}$

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Figure 1. Illustration of decision making process in the Markov Decision Process. This figure illustrates how the MDP chooses the optimal action (treatment decision) at each decision epoch. The transition probabilities from the current state to the next are determined by which action is taken, and each transition is associated with corresponding rewards. This illustration has three actions in different colors. The numbers in each parenthesis are the transition probability and reward associated with each action. The MDP chooses an action that will maximize total rewards by calculating expected rewards from each action over the simulated horizon.

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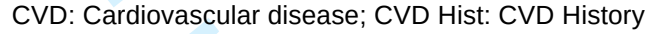
eFigure 2. Schematic of health states in the Markov Decision Process



CVD: Cardiovascular disease; CVD Hist: CVD History

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eFigure 3: Illustration of a single patient receiving different treatments under MDP-based treatment (MDPT) versus current guidelines. A single patient with a certain set of demographic features and CVD-related covariates is recommended for different treatment regimens. JNC8 and Intensive JNC8 recommend no treatment. MDPT recommends a half dose of beta-blocker for this patient with a blood pressure that is below the current targets due to his/her CVD-related covariates that indicate high risk of CVD.

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eFigure 5. Calibration results: stroke incidence. We considered our targets were met if the projected incidence fell within the interval between the estimates from Framingham Heart Study (FHS) and the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS).

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eFigure 7. QALYs in eachdisease state overpatient lifetimes

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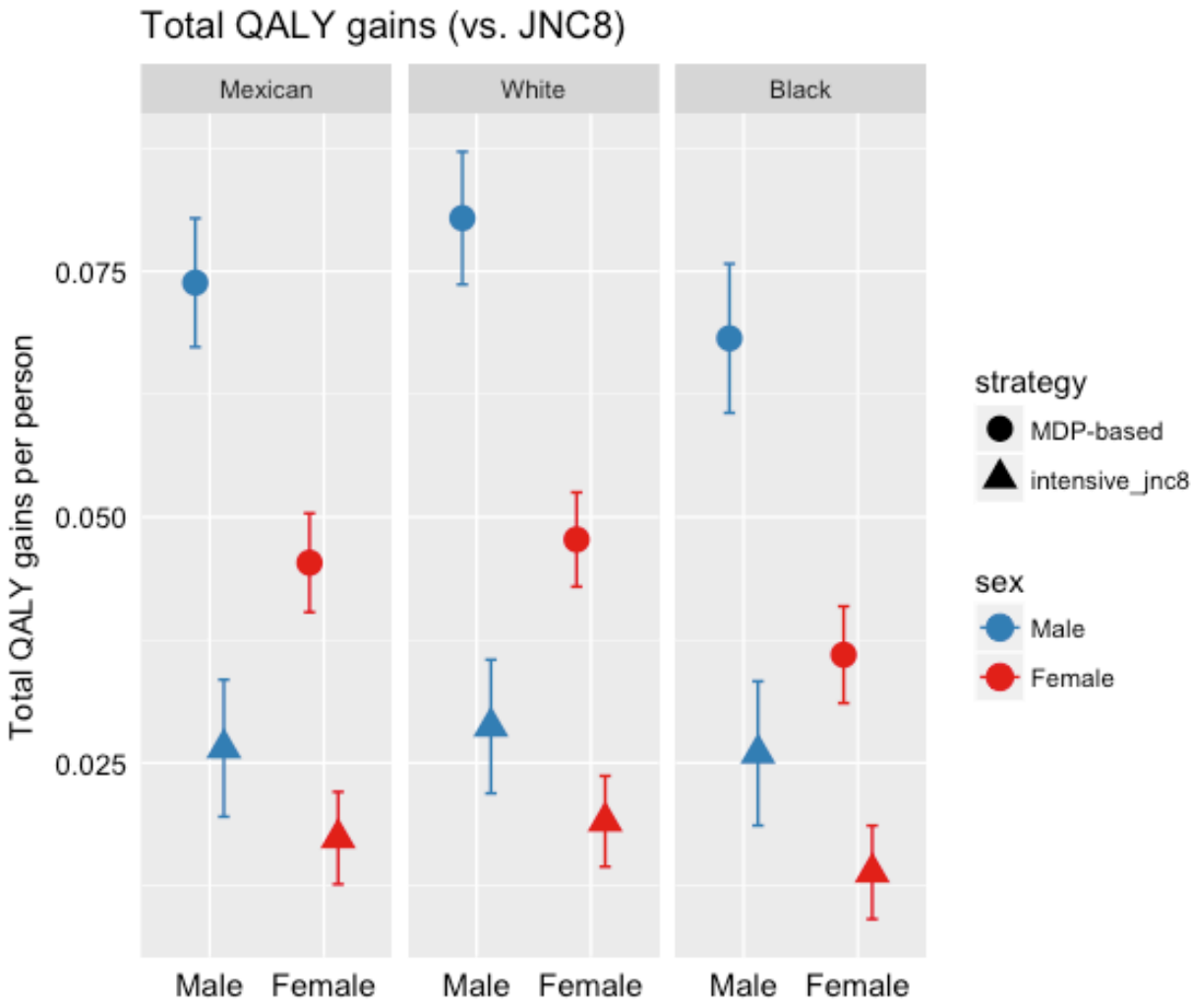
eFigure 8. Total QALY gains over patient lifetimes for the Intensive JNC8 strategy and the MDP-based treatment strategy, compared to the JNC8 strategy



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With CVD History

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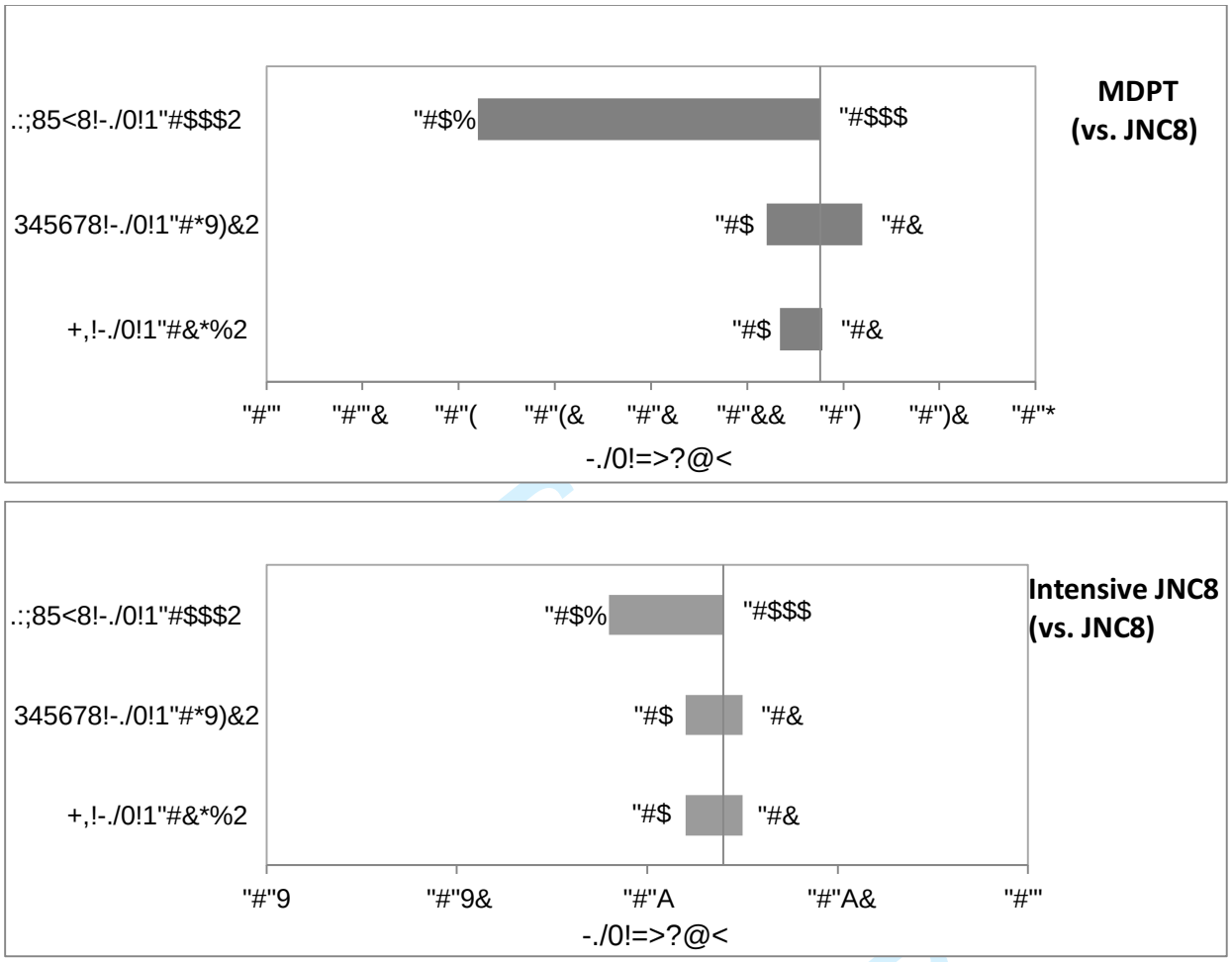
eFigure 10. Sensitivity analysis: QALY gains from the MDP-based treatment (MDPT) strategy and the Intensive JNC8 strategy (vs. JNC8). The vertical lines represent the QALY gains in the base case analysis, and the horizontal bars represent the variation of the QALY gains given variations of parameters. The numbers at each end of the bars represent the lower and upper bounds of the value used for each parameter.



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Stroke QALY weights (dynamic: MDP-based)

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eTable 1. Risk of Adverse Events from Medications: Percentage of Patients with One or More Symptoms Attributable to Treatment*[1]

Medication	Half dose		Standard dose		Twice standard dose	
	Mean	SD	Mean	SD	Mean	SD
ACE- I	3.9	3.88	3.9	2.24	3.9	2.09
ARB	-1.8	4.28	0	1.79	1.9	3.83
Beta-blocker	5.5	2.6	7.5	1.79	9.4	2.6
CCB	1.6	2.65	8.3	1.79	14.9	2.95
Thiazide	2	2.14	9.9	1.68	17.8	3.21

*Calculated as difference between treated and placebo groups in proportion of participants who developed one or more symptoms, excluding headaches, which were significantly less common in people receiving treatment

Note: The adverse event rates from higher doses were linearly extrapolated up to 4 standard doses.

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eTable 2. Comparison of Simulated Population and NHANES, 2003-2014

Characteristics [Mean or N (%)]	Simulated population	NHANES	P-value
Age (years)	50.52	49.20	< 0.001
Male	50.2%	50.9%	0.001
Race/ethnicity			
Mexican American	11.0%	11.5%	0.002
Non-Hispanic White	63.4%	62.9%	< 0.001
Non-Hispanic Black	25.4%	25.5%	0.001
MI History	4.26%	4.26%	0.040
Stroke History	3.26%	3.00%	<0.001
SBP	124.1	122.7	0.010
Total cholesterol	197.1	195.0	<0.001
HDL cholesterol	52.73	53.01	<0.001
Smoking prevalence	21.0%	20.8%	<0.001
Type 2 diabetes prevalenc	13.5%	13.1%	<0.001
Kidney disease history	18.9%	22.3%	0.030

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eTable 3. Quality-of-Life and Cost Estimates for Disease States and Adverse Events

By disease states and adverse events, mean (sd)

Disease states	Quality of life	Sources
MI	0.578	[4, 10]
Stroke	0.7165	[4, 10, 11]
Post CVD	0.9	[4, 10]
Adverse event	0.999	[4]

Disease states	Annual cost	Sources
MI	$44,267	[11]
Stroke	$23,254 (1400)	[11]
Post CVD	$5,208 (356)	[12]
Adverse event	(see below)	

Annual costs of medications and associated adverse events[11, 13]

Dose	Antihypertensive drug costs	Costs of adverse events*
0.5 standard doses	gamma(1.24, rate = 0.01)	$65.92
1.0 standard dose	gamma(1.66, rate = 0.01)	$131.40
1.5 standard doses	gamma(0.216, rate = 0.001)	$162.63
2.0 standard doses	gamma(0.238, rate = 0.001)	$193.87
2.5 standard doses	gamma(0.298, rate = 0.001)	$225.93
3.0 standard doses	gamma(0.357, rate = 0.001)	$258.05
3.5 standard doses	gamma(0.430, rate = 0.001)	$258.05
4.0 standard doses	gamma(0.496, rate = 0.001)	$258.05

* Costs of adverse events were estimated based on hospitalization average cost (used for infrequent hospitalized drug-related adverse events) and high costs (used for rare hospitalized drug-related adverse events) and incidence rates of serious adverse effects of medication (common, infrequent, and rare).

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eTable 4. Comparison of MDP-based treatment (MDPT) vs. Intensive JNC8 Strategies

	Patients treated similarly by both Intensive JNC8 and MDPT strategies	Patients treated more intensively by MDPT strategy	Patients treated more intensively by Intensive JNC8 strategy
% of population	19.1	17.6	63.3
Mean initial 10-year CVD risk (%)	14.5	18.6	12.7
Mean post-10 years of treatment 10-year CVD risk (%)	14.6	14.8	14.6
QALY loss saved from CVD events, per 1000 patients treated, compared to Intensive JNC8	1.85	2.17	1.25
QALY loss saved from adverse events, per 1000 patients treated, compared to Intensive JNC8	0.03	-0.04	0.07
Total QALYs saved, per 1000 patients treated, compared to Intensive JNC8	43.4	46.8	31.7

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eTable 5. Baseline MI History Prevalence(%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	0.00	NA	0.72	0.25	6.92	1.04
	NH White	0.21	0.04	2.31	0.18	15.42	0.48
	NH Black	0.00	NA	4.43	0.61	12.11	0.75
Female	Mexican	0.00	NA	1.26	0.29	4.11	0.60
	NH White	1.34	0.22	1.32	0.16	8.71	0.38
	NH Black	0	NA	0	NA	5.91	0.06

eTable 6. Baseline Stroke History Prevalence(%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	0.00	NA	1.91	1.89	9.43	3.94
	NH White	0.14	0.13	0.42	0.24	6.51	1.48
	NH Black	0.00	NA	1.98	1.72	12.61	3.76
Female	Mexican	0.00	NA	1.51	8.66	2.68	2.30
	NH White	1.05	1.04	1.69	0.61	7.95	1.72
	NH Black	0.33	0.32	4.49	2.32	8.02	2.95

eTable 7. Baseline Hypertension Medication Use Prevalence(%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	1.46	1.48	9.75	5.26	41.66	8.53
	NH White	3.95	1.49	14.25	2.35	52.41	2.41
	NH Black	5.76	1.41	33.54	4.48	62.41	3.91
Female	Mexican	7.88	5.24	6.47	3.48	47.86	10.54
	NH White	0.81	0.64	24.70	3.30	54.23	3.42
	NH Black	9.48	3.41	43.57	4.95	75.36	6.23

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eTable 8. Baseline Systolic Blood Pressure (mmHg)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	121.4	1.2	124.1	3.2	135.1	7.6
	NH White	120.5	1.2	124.4	1.2	131.1	1.1
	NH Black	123.5	1.0	128.5	1.4	136.8	1.2
Female	Mexican	110.6	1.4	120.3	2.4	138.5	3.9
	NH White	109.9	0.7	121.2	1.1	135.3	1.3
	NH Black	113.8	1.3	128.5	1.9	140.4	1.9

eTable 9. Baseline Total Cholesterol (mmol/L)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	179.1	5.4	208.8	6.8	187.8	8.1
	NH White	191.5	4.4	206.4	2.1	187.8	1.4
	NH Black	182.3	3.3	190.8	5.0	184.9	4.6
Female	Mexican	187.2	5.6	208.9	6.7	208.6	9.5
	NH White	189.8	2.9	209.6	2.9	208.5	2.4
	NH Black	182.9	2.8	201.4	3.9	206.9	5.6

eTable 10. Baseline HDL Cholesterol (mmol/L)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	44.8	1.8	52.8	3.7	48.4	4.4
	NH White	47.3	1.1	49.1	0.8	51.2	0.6
	NH Black	49.5	1.5	54.9	2.7	53.0	0.7
Female	Mexican	58.7	2.4	55.7	4.1	53.3	2.4
	NH White	58.5	1.0	60.0	0.9	63.0	1.0
	NH Black	59.4	1.6	62.4	1.7	64.7	3.2

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Dynamic Treatment Selection and Modification for Personalized Blood Pressure Therapy using a Markov Decision Process Model: A Cost-effectiveness Analysis

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The probability that a person transitioned from healthy to either MI or stroke was based on equations previously validated in several diverse cohorts containing more than 23,000 subjects, and subsequently against prospective patient-level data on blood pressure and CVD mortality from more than 1 million adults (Appendix eText 3).[17-21] The equations are a function of the set of covariates: age, sex, race/ethnicity (Centers for Disease Control and Prevention categories of non-Hispanic White, non-Hispanic Black, Mexican American, and Other), initial systolic and diastolic blood pressures, total and high-density lipoprotein (HDL) cholesterol, tobacco smoking status, current treatment with blood pressure medication, type 2 diabetes status, and previous history of MI or stroke. Covariate values were updated annually to reflect linear age- and secular time-trends. The degree to which a given SBP reduction from a medication at a particular dosage reduced the risk of MI or stroke was calculated based on a prior meta-analysis of randomized trials.[19] Deaths attributable to MI/stroke and competing risks were taken into account as a function of age and sex (Appendix eText 4).[21, 22] The probability of severe adverse events (significant side effects leading to clinically significant disability or hospitalization) was determined by a prior meta-analysis, specific to patient covariates, blood pressure medication choice and dosage (Appendix eTable 1).

We simulated 10,000 adults aged 18 to 85 years old over their lifetimes, by repeated sampling with replacement from the correlated covariates in the National Health and Nutrition Examination Survey (NHANES, 2003-2014, = 74,501). We used NHANES survey weights to generate sampling distributions for each covariate,[23] and used multivariate sampling with copulas to capture the correlations among the covariates.[24] To estimate untreated blood pressure for those NHANES participants on antihypertensive medication, we back-calculated the pretreatment blood pressure for those reporting current blood pressure treatment, using a previously published

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procedure.[3] To ensure face validity, MI and stroke incidence rates were compared through backwards projection while maintaining current blood pressure medications listed in NHANES to years 2003 and 2014, to compare to estimates from the Atherosclerosis Risk in Communities study, the Greater Cincinnati/Northern Kentucky Stroke Study, and independent cohort studies from the National Heart Lung and Blood Institute (NHLBI).[20, 25, 26] The validation exercise showed that the model was within 5% absolute error from actual observed incidence rates of MI and stroke (Appendix eFigures 4-5, eTable 2).

We compared three treatment strategies: (1) JNC8 based on current US guidelines, targeting blood pressure <140/90 mmHg for persons with chronic kidney disease or diabetes, or persons <60 years old, and BP<150/90 mmHg for persons ≥60 years old and without chronic kidney disease or diabetes;[5] (2) Intensive JNC8 (JNC8 modified by results of the recent SPRINT trial), specifically lowering SBP to 120 mmHg among high-risk patients (those with ≥15% 10-year risk of combined MI and stroke) but using the same blood pressure targets as in JNC8 for others;[6, 15] and (3) an MDP-based treatment (MDPT) strategy that determines optimal medication choices based on the MDP (Figure 1). To restrict our analysis to the range of possibilities considered safe and effective, we set the number of blood pressure medications to a maximum of 4 per person, and stopped augmentation of blood pressure treatment if a simulated patient's systolic blood pressure fell below 120 mmHg.[3, 27]

As suggested in JNC8 guidelines, for all treatment strategies, initial blood pressure medication choice included a thiazide, calcium channel blocker (CCB), ACE inhibitor (ACE-I), or angiotensin receptor blocker (ARB) in the general non-Black population, or a thiazide or CCB for the general Black population. In the JNC8 and Intensive JNC8 strategies, if the target blood

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pressure was not reached within one month, the dosage of the medication was increased, or another medication was added.

We used two outcome metrics to compare the treatment strategies: (i) total discounted QALYs over the lifetime of each simulated individual; (ii) the incremental cost-effectiveness ratio of the MDPT strategy versus JNC8, and of Intensive JNC8 versus JNC8.

Following current cost-effectiveness guidelines[28, 29], costs and QALY estimates were integrated over the life-course for all simulated individuals, starting in 2017. Costs of medications and associated adverse events were obtained from the National Inpatient Sample survey and Red Book (Appendix eTable 3).[30, 31] Annual disease-specific healthcare costs and the disutility of disease states and side effects to calculate QALYs were based on large-scale survey data (Appendix eTable 3).[32, 33] Costs were expressed in 2017 US Dollars using the Consumer Price Index[34],and QALYs were discounted at 3% annually.

We performed sensitivity analyses to assess key sources of variability in the outcome estimates, specifically by varying disutility weights for disease states: treatment-related disutility (QALYs per medication per year of treatment associated with serious adverse events) was varied from 0.001 to 0.02. The disutility from CVD events (separately for MI and stroke) was varied across the range from 0.5 to 0.9 based on variations observed in patient survey data.[3, 35-37] We performed uncertainty analyses across all simulations by re-running the full model while repeatedly Monte Carlo sampling with replacement 10,000 times (thus 10,000 discrete runs) from the probability distributions of all input parameters.[38]

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All analyses were performed in (version 3.2.1, The R Foundation for Statistical Computing, Vienna), with model code available at https://sdr.stanford.edu concurrent with publication.

Results

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Over a simulated life course, the MDPT strategy tended to treat patients more intensively than JNC8 (Figure 2). The MDPT strategy prescribed 2.34 (95% CI: 2.33-2.34) medication doses per person, versus 2.22 (95% CI: 2.21-2.22) under JNC8 (Table 2). The greatest increases in dosages from the JNC8 to the MDPT strategy were among high-risk individuals aged less than 60 years; patients were treated more intensively earlier in life under the MDPT strategy when their initial 10-year CVD risk was higher (Figure 2 and Table 3). These increases in dosages were more prominent among Blacks (eFigure 6). By starting to treat patients more intensively earlier in life based on individual risks and estimated benefits, the MDPT strategy averted more CVD events over the course of life, preventing more intensive treatment requirements later in life and thereby saving QALYs (eFigure 7 and Table 3).

Treated individuals experienced 19.03 (95% CI: 19.01-19.05) and 18.97 (95% CI: 18.95-18.98) total discounted QALYs per person under the MDPT and JNC8 strategies, respectively. Compared to JNC8, the MDPT strategy gained 0.06 (95% CI: 0.04-0.08) QALYs per person, and was cost-saving with estimated discounted savings of $1,187 (95% CI: 1,168-1,206) per person. The QALY gains would be realized largely from averting CVD events among high-risk individuals by treating them earlier with relatively lower treatment dosages than they would have received later in life.

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The projected QALY gains were larger among men than women because larger shifts from the JNC8-recommended to MDPT-recommended treatments tended to intensify men's blood pressure treatments due to their higher risk and higher benefit, and in turn further reduce men's MI and stroke risks (Appendix eFigures 7-8).

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The Intensive JNC8 strategy tended to treat patients more intensively later in life than the MDPT strategy (Figure 2). Over the course of life, individuals under the Intensive JNC8 strategy received 3.18 (95% CI: 3.18-3.19) doses on average per person per day as compared to 2.34 (95% CI: 2.33-2.34) doses under the MDPT strategy. Compared to the MDPT strategy, 63.3% of the simulated population received higher dosages over the course of life under the Intensive JNC8 strategy although the initial 10-year CVD risk of those people was significantly lower than that of people treated more intensively by the MDPT strategy (Appendix eTable 4). By treating based on individual risks, the MDPT strategy tended to treat patients more intensively earlier in life and less intensively at older ages (Figure 2).

The Intensive JNC8 strategy was dominated by the MDPT strategy. Treated individuals under the Intensive JNC8 strategy experienced 0.04 (95% CI: 0.02-0.06) fewer total discounted QALYs per person than those treated under the MDPT strategy, and at higher costs. By waiting to control blood pressure later in life under the Intensive JNC8 strategy, cumulative exposure to high blood pressure from young adulthood to middle age resulted in higher QALY loss due to CVD events (Appendix eFigure 7).

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Among Black populations, CCBs and ARBs were the most prescribed medications as the first and second medications in both strategies. In addition, thiazides and ACE-Is (or beta-

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blockers and thiazides for people with prior CVD history) were prescribed the most as the third and fourth medications, respectively, in the MDPT strategy (Appendix eFigure 9).

We measured individuals' SBP levels achieved under each treatment strategy over the simulated period. SBP levels of individuals under the MDPT strategy remained the lowest among individuals aged less than 60 years, at an average of 118.1 mmHg (95% CI: 117.6-118.6) in patients aged 18-39 years old and 126.4 mmHg (95% CI: 125.6-127.2) in patients aged 40-59 years old (Figure 3). For patients older than 60 years old, SBP levels were lowest under the Intensive JNC8 strategy, 139.4 mmHg (95% CI: 138.8-140.0) as compared to 148.9 mmHg (95% CI: 148.0-149.8) under the MDPT strategy.

None of the sensitivity analyses substantially changed our fundamental finding of benefits and cost savings from the MDPT strategy compared to the Intensive JNC8 and JNC8 strategies (Appendix eFigures 10 and 11). The QALY weight for the adverse event states in our base-case analysis was 0.999, which is a conservative estimate for serious adverse effects of treatment.[3, 36] When we varied adverse event state QALY weights from 0.98 to 0.999, the lowest estimated QALY gain from the MDPT strategy compared to the JNC8 strategy was 41.0 (95% CI: 21.4-60.6) QALYs per 1000 persons (Appendix eFigure 10). When a QALY weight of 0.98 was assumed for the adverse event states, treated individuals under the Intensive JNC8 did not experience significantly different QALYs than JNC8. With lower QALY weights for adverse events, patients with a CVD history did not have substantially different dose levels under the MDPT strategy (Appendix eFigure 10), but patients without CVD history had lower dose levels than under Intensive JNC8 and JNC8.

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Next, we varied MI and stroke QALY weights from 0.5 to 0.9 for either or both of the disease states. The QALY gains from the MDPT strategy compared to the JNC8 strategy ranged from 56.7 (95% CI: 36.4-75.6) to 59.0 (95% CI: 39.4-78.6) QALYs per 1000 persons for MI and from 56.0 (95% CI: 37.1-76.3) to 61.0 (95% CI: 41.4-80.6) QALYs per 1000 persons for stroke (Appendix eFigure 10). Treatment dose levels were not significantly affected by varying QALY weights for adverse events, stroke, or MI (Appendix eFigure 11).

Discussion

Personalizing medical decisions will require considering an increasingly complex variety of individual-level covariates, treatment effect modifiers, and risks and benefits of treatment alternatives. Personalizing decisions is recommended by current CVD management guidelines, as with guidelines for many other conditions, but how to operationalize such guideline statements remains unclear because guidelines generally recommend therapy based on broad categories of features rather than the complex combinations of features that any individual would have.[39] As a result, simple rules of thumb (such as specific blood pressure levels or medication of choice for all people with diabetes) are favored by physicians due to the burden of performing complex risk/benefit calculations at each step of the treatment decision-making process.[3, 40] Personalizing decisions may therefore be made more optimal through the use of automated computational strategies to incorporate individual patient data into individualized treatment recommendations. While several studies have previously suggested that blood pressure therapy should involve calculations of patient risks and benefits, using a Markov simulation model, this is the first time—to our knowledge—that a systematic, comprehensive, and automated calculation approach has been proposed to achieve this objective by incorporating patient heterogeneity in risk factors and responses to treatment (probabilistically), and recommending

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detailed treatment suggestions (doses and types of medication).[3, 4] From a clinical perspective, our analysis advances the current treatment guidelines beyond the decision of whether to treat high blood pressure because both type and dosage of medication are critical decision points.[5, 41]

We developed an MDP-based model to optimize treatment of blood pressure medication and dose selection, based on currently best-available meta-analytic data and risk calculations. While there remains considerable uncertainty in any model-based treatment selection, we found that even when repeatedly sampling over uncertainty ranges of blood pressure treatment benefit and risk, a substantial improvement could be made over current blood pressure management guidelines not only for individuals, but also for the overall population. Our study suggests that initiating blood pressure management earlier for young and middle-aged adults with prehypertension substantially reduces MI and/or stroke occurrences over the course of life; the cumulative QALY benefit from the MDP-based approach was primarily from long-term chronic outcomes of high blood pressure leading to long-term sequelae of MI and strokes. This is particularly notable in light of doubts that personalized medicine can improve population health.[31, 42] We open-sourced our code to permit replication and extension to other disease processes that similarly involve risk/benefit calculations among a large number of potential treatments with different treatment effects and side-effect probabilities among different types of patients, as is currently the case with type 2 diabetes, cancer, and HIV.[43, 44]

As with any modeling exercise, our study is limited by the quality of its input data and assumptions. First, we modeled the effects of blood pressure treatment medication based on published data, assuming that the health benefits of medications were mediated through changes in blood pressure as per current physiologic understanding. Second, we used data from NHANES, which are subject to the limitations of survey studies, including recall biases,

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acceptability biases, and underreporting that may lead to mis-estimation of baseline covariates and limits the analysis to the civilian (non-institutionalized) US population.[45] Third, we did not incorporate compliance/adherence parameters in the model because our purpose in this model is to compare how a change in guidelines from the current guidelines to the MDP-based strategy would affect overall population-level outcomes under the ideal treatment condition. Adding in a compliance/adherence parameter would simply linearly scale the outcomes to the proportion of patients who adhere, unless we have further data from [not yet extant] randomized trials suggesting that patients would adhere differently to treatment regimens found using the MDP-based approach than to regimens identified under the current guidelines. We suggest that such randomized trials and real-world studies should be performed now that a proof-of-concept model is available, to gather empirical data comparing adherence rates and observed outcomes between the MDP-based and current guideline approaches. Fourth, although we performed uncertainty analyses by sampling from distributions around the input parameter data sources, we cannot capture all possible uncertainties in the model. We focused on MI and stroke because of high-quality, validated risk equations for predicting these outcomes and their risk reduction through therapy. Although congestive heart failure and kidney diseases may also be averted, we did not model them due to the lack of robust and validated risk equations; however, their impact is considered proportional to the impact on MI and stroke[3], and thus should not affect our comparative effectiveness analysis. Ignoring these potential benefits makes our cost-effectiveness estimates conservative. Fifth, one of the largest ongoing debates in personalized medicine is the fact that model-based personalization may offer incremental gains beyond large standardized guidelines, but at the risk of producing a "black box." A larger discussion must take place in the literature about the benefits and risks of such model-based personalization before

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such measures are considered for practice. A next logical step for research is to perform a head-to-head randomized pilot trial to compare usability, interpretability, patient and provider reactions, and patient safety of current guidelines versus our personalized blood pressure treatment selection tool. We note that the result of a small gain in QALYs is expected in the case of blood pressure treatment because only a small subset of patients experience a CVD event; this gain, although small, is cost-saving from a societal perspective. Lastly, we chose MDP over other reinforcement learning approaches due to its simplicity and flexibility. Perfect knowledge about a patient's states under MDP is a strong assumption, but we chose to use MDP since it is often tractable to solve (exact solution) and relatively easy to specify, and because CVD health states are objectively observable by clinicians under nearly all circumstances (unlike with some other diseases).[46-50] Partially observed MDPs (POMDPs) are more complex than MDPs and are often computationally intractable. The use of POMDP for determining personalized blood pressure treatment guidelines, which may yield a more realistic but less tractable model, is an area for future research.

The next logical step for analysis is to prospectively test the MDP-based model in clinical settings to identify safety, adoptability, and impact on patient outcomes. Existing clinical guidelines are typically easy for clinicians to interpret because they involve univariate decisions. To make use of the MDP-based approach, clinicians would need to shift conceptually from a univariate to a multivariate decision process as well as accept computationally complex "black box" results (as they do currently with some imaging and pathological diagnostic guidelines). An additional logical step for future research is to identify whether QALY values co-vary meaningfully among individuals as a function of their risk, age, and prior treatment. Use of personalized QALYs would enable more personalized decision-making rather than assuming that

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QALY weights of CVD outcomes or serious adverse events are consistent across the population. For example, some persons may favor lower risk of side effects than CVD events if they are concerned about short-term suffering rather than long-term mortality (e.g., if they are near the end of life).

While these remain important topics for future research, our current findings indicate that blood pressure treatment policies informed by a Markov Decision Process framework may improve patient outcomes compared to the use of standardized target-based guidelines, by accounting for individual-patient covariates in treatment decision-making processes, and are likely to be cost-saving compared to current guidelines.

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Table 1. Model Parameters and Sources

Parameters	Source
Population size of demographic cohorts	NHANES 2003-2014
Risk of MI or stroke by demographic group (Appendix eText 3)	Model-based estimates from meta-analysis data[19-21]
Baseline MI history prevalence (Appendix eTable 5)	NHANES 2003-2014
Baseline stroke history prevalence (Appendix eTable 6)	NHANES 2003-2014
Baseline hypertension medication use prevalence (Appendix eTable 7)	NHANES 2003-2014
Baseline systolic blood pressure (Appendix eTable 8)	NHANES 2003-2014
Baseline total cholesterol (Appendix eTable 9)	NHANES 2003-2014
Baseline HDL cholesterol (Appendix eTable 10)	NHANES 2003-2014
Baseline smoking prevalence (Appendix eTable 11)	NHANES 2003-2014
Baseline Type 2 diabetes prevalence (Appendix eTable 12)	NHANES 2003-2014
Baseline chronic kidney disease prevalence (Appendix eTable 13)	NHANES 2003-2014
MI or stroke mortality rate (Appendix eText 4)	Model calibration to national data[19-21]
All-cause mortality rate	CDC[22]

NHANES = National Health and Nutrition Examination Survey; MI = myocardial infarction; CDC = Centers for Disease Control and Prevention; HDL = High-density lipoprotein

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Table 2. Differences in Treatment (Mean (se)), and Cost-Effectiveness Analysis

Treatment strategy	Treatment dose	MI events (%)	Stroke events (%)	Total QALYs	Total cost ($)	Incremental per person QALYs vs. JNC8	Incremental per person cost ($) vs. JNC8	ICER vs. JNC8
JNC8	2.22 (0.001)	33.21 (0.11)	35.60 (0.11)	18.97 (0.01)	16,459 (10.68)	-	-	
Intensive JNC8	3.18 (0.001)	32.79 (0.11)	34.99 (0.11)	18.99 (0.01)	17,385 (11.52)	0.02	926	Dominated
MDP-based treatment (MDPT)	2.34 (0.002)	29.99 (0.11)	32.63 (0.11)	19.03 (0.01)	15,272 (9.81)	0.06	-1,187	Cost-saving

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Table 3. Comparison of MDPT vs. JNC8 Strategy

	People treated similarly* by both JNC8 and MDPT strategies	People treated more intensively by MDPT strategy	People treated more intensively by JNC8 strategy
% of population	12.4	47.8	39.8
Mean initial 10-year CVD risk	13.4	15.2	13.1
Mean post-10 years of treatment 10-year CVD risk	14.1	14.7	14.7
Averted **QALY loss from CVD events, per 1000 patients treated, compared to JNC8**	1.39	3.01	1.54
Averted **QALY loss from adverse events, per 1000 patients treated, compared to JNC8**	-0.03	-0.09	-0.02
Total QALYs saved, per 1000 patients treated, compared to JNC8	40.0	74.9	44.6

MDPT = Markov Decision Process-based treatment; JNC8 = Eighth Joint National Committee treatment strategy

*"Treated similarly" was defined as rounded mean treatment dose level over the patient's lifetime being the same between the JNC8 and MDPT strategies

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Figure 1. Model schematic

* “High-risk” was defined the same as SPRINT and ACCORD enrollment eligibility criteria except for type 2 diabetes status

Figure 2. Treatment dose levels under each treatment strategy

Figure 3. Mean systolic blood pressure (SBP) levels of individuals achieved under each treatment strategy

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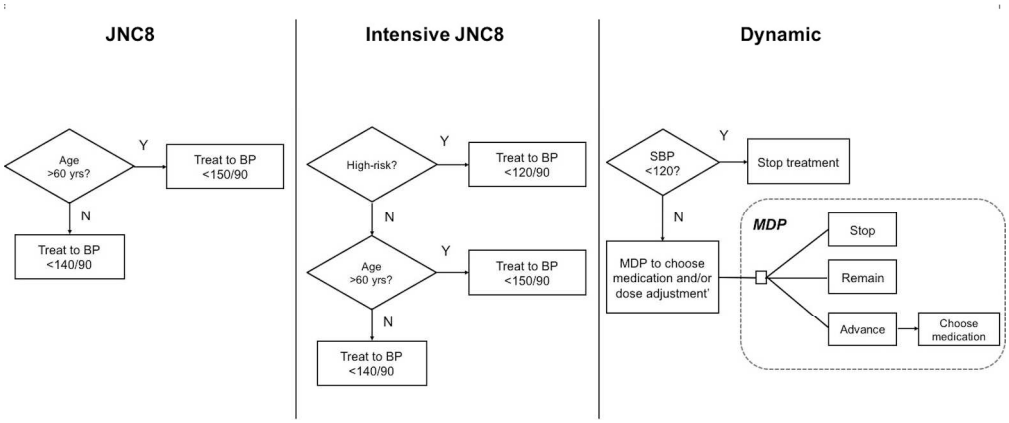
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Age >60 yrs?
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Intensive JNC8
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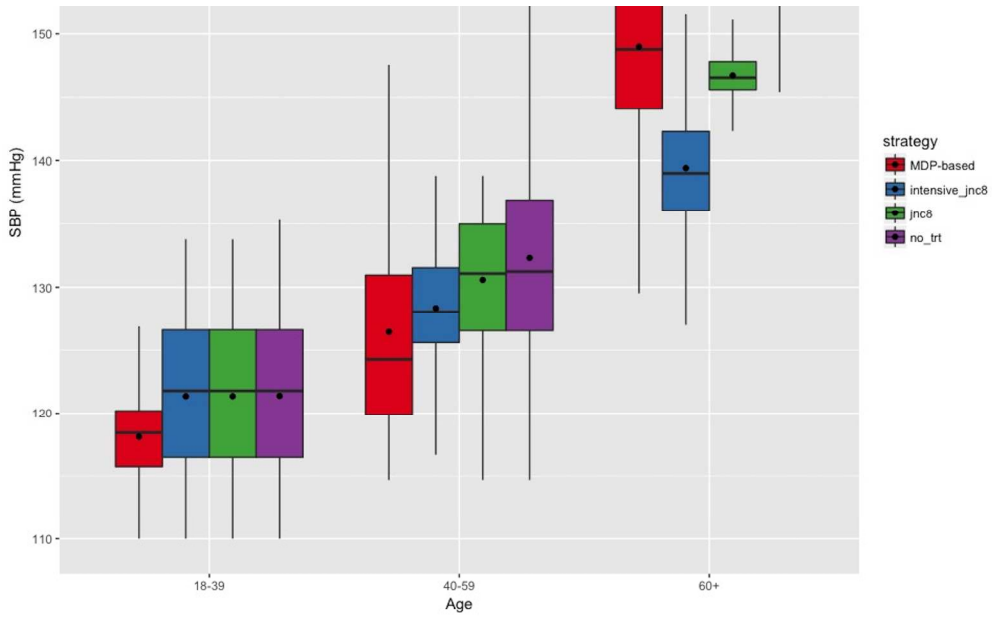

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eText 1. Model formulation

MDP formulation

Herewe present the formulation of the MDP model. The simulation code is available at https://sdr.stanford.edu/. The MDP model is characterized by a state space, action space, transition probabilities, and rewards. A patient may enter one of 7 health states, as illustrated in eFigure 1: (1) Well; (2) Adverse event without CVD history; (3) MI; (4) Stroke; (5) Post CVD; (6) Adverse event with CVD history; (7) Death. Model notation is shown below. The action space consisted of a finite set of possible actions (treatment decisions). A patient could stop a medication treatment, remain on the current medication treatment(s) and dose, or change (e.g., add) a medication treatment (by increasing a dosage of a current medication, and/or changing the medication). We did not include decreases in dosage in our action space to mimic how current clinical practice (including the protocol in randomized trials) is conducted. Usually blood pressure medication is prescribed, with increases in dosage if necessary, until the patientÕs blood pressure meets the target blood pressure goal. Once the target blood pressure is reached, the patient no longer changes medication dosage and typically stays on the same dosage for life. The objective of the MDP is to determine the optimal treatment strategy π^* for a single patient that maximizes the patientÕs expected discounted quality-adjusted life years (QALYs) over a simulated time horizon. The MDP chooses an action to maximize the expected gains by calculating transition probabilities and rewards (discounted QALYs) associated with each action as illustrated in eFigure 2.

Treatment effectiveness was modeled to be mediated through systolic blood pressure (SBP) reduction based on a meta-analysis of 147 randomized clinical trials, in which SBP reduction from treatment was found to be a function of the number of prescribed drugs and the

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dosage-level of the drugs.[1] The treatment dose scale and medications used in our model were based on that meta-analysis.[1] In our model, patients can take up to 4 different medications from among the following: angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), beta-blocker, calcium channel Blocker (CCB), and thiazide diuretic. The treatment dose scale is as follows:

0 – No treatment
0.5 – One drug, ½ dose
1 – One drug, 1 dose
1.5 – Two drugs, ½ doses
2 – Two drugs, 1 dose each
2.5 – Three drugs, ½ doses
3 – Three drugs, 1 dose each
3.5 – Four drugs, ½ doses
4 – Four drugs, 1 dose each

Transition probabilities, $P_a(s, s')$, are functions of the patient's post-treatment CVD risk, $r_a(s)$ → $r_a(s) = RR(s)*r(s)$; the likelihood of death from a CVD event, $\rho(s)$; the likelihood of non-CVD death, $\varphi(s)$; the likelihood of side effects from treatment, $\beta_{a,m}(s)$.

The transition probabilities, $P_a(s, s')$ are updated in every time step (i.e., every month). At each time step, individuals are faced with either continuing with the current treatment option or advancing to the next level. When transitioning from s to s' state, rewards are given by:

$$R_a(s, s') = Q_a(s, s')$$

At each time-step, π will contain the solution and $V(s)$ will contain the discounted sum of the rewards to be earned (on average) by following that solution from state s. The Bellman value function gives the maximized expected QALYs when in state s:

$$V(s) = \sum_{s'} P_a(s, s')(R_a(s, s') + \lambda V(s'))$$

The optimal policy maximizes the sum of expected QALYs over the time horizon:

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$$\pi^*(s) = argmax_a\{\sum_{s'} P_a(s,s')(R_a(s,s') + \lambda V(s'))\}.$$

MDP Model Notation

Variable	Description
t	Time index; t = 0,1,É, T
$d \in D$	Treatment dose options A=(1,É ,9)
$m \in M$	Number of treatment drugs M. M=(1,É,4)
$b_{min} \in R+$	Minimum allowable SBP
$g \in G$	Multidimensional state of the patient represented by the number of remaining decision epochs in the planning horizon, risk factors including demographic information for the patient (e.g. age, sex, smoking status) CVD competing risk factors (pretreatment SBP, DBP, total cholesterol, HDL cholesterol, smoking status, hypertension treatment status, diabetes status, CVD history) n = 0,…, N, the number of remaining decision epochs p represents patient demographic information (age, sex, race, income) $b \in$ R+ denotes the pretreatment SBP c represents patient CVD competing risk factor $s \in$ [1, É,7] denotes the patient health state g = (n; p; b; c; s)
$RR(s) \in$ [0,1]	Relative risk factor when in state s
$r(s) \in$ [0, 1]	Patient's pretreatment risk of a CVD event in state s
$r_a(s) \in$ [0, 1]	PatientÕs post treatment risk of a CVD event in state s with action a; $D(s)*r(s)$
$P_a(s,s')$	Transition probabilities from state s to s'
$\varphi(s) \in$ [0, 1]	Probability of death from non-CVD cause given the patientÕs post-treatment CVD risk when in state s
$\rho(s) \in$ [0, 1]	Probability of death from a CVD event when in state s, given that the patient had a CVD event
$\beta_{a,m}(s) \in$ [0, 1]	Probability of experiencing side effects (adverse events) in s state
$Q_a(s,s')$	QALYs associated with transition from s to s'
λ	Discount rate for costs and health benefits

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Microsimulation model formulation

We developed a microsimulation model at the level of the individual. The model is stochastic, we sample from probability distributions of input parameters to generate a distribution of outcomes. The model is run in discrete time steps over the course of individuals' lifetimes from 2017. Key parameters and data sources are summarized in eTables 1-3.

We classified the synthetic population in this model by combinations of a few key demographic characteristics: age (18-39, 40-59, 60-85 years old), sex, and race/ethnicity (NHANES categories of non-Hispanic white, non-Hispanic black, Mexican American or other). Because NHANES comprises repeated cross-sectional data, we had to construct a synthetic population to account for the survey weights. We generated 10,000 individuals, following pretreatment guidelines, for each cohort defined by the combinations of these characteristics. We re-ran the model 10,000 times while repeatedly Monte Carlo sampling from the probability distributions of all input parameters to capture uncertainties in our estimates.[2] Baseline characteristics between the simulated population and NHANES participants were compared using MANOVA (eTable 2).[3]

Baseline CVD risk factors and prevalent disease cases were assigned to each simulated individual by repeated Monte Carlo sampling from the probability distributions of each of these variables in NHANES, specific to each demographic group. The joint probability distributions of these risk factors were accounted for using multivariate sampling with copula functions, which allows us to capture how these factors are dependent. This procedure takes into account the correlation between risk factors. To account for individuals aging, we tracked the age of each simulated individual over the simulation period, and updated each individual's health metrics to account for age-specific health risks by preserving the individual's rank in the population

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distribution to account for the stability of risk over time and different survival probability.

eText 2. Effects ofhypertension medicationon blood pressure and CVDrisks

We estimated the effect of blood pressure medications on lowering blood pressure as a function of dose based on a meta-analysis of 147 randomized placebo controlled trials of blood pressure-lowering drugs in fixed dose,[4] which showed that the five main classes of blood pressure-lowering drugs produce similar reductions in blood pressure. In our model, patients were allowed to take only up to full doses of 4 different medicines, given current data suggesting that increasing blood pressure medications beyond 4 full doses has been found to increase side effects/adverse effects without providing any incremental benefit for patients.[5] In the JNC8 and Intensive JNC8 strategies, even if the patients' blood pressure levels do not meet the target blood pressure goals, they were not allowed to receive more than 4 full doses of medications. In the MDP-based treatment (MDPT) strategy, patients did not have an option to increase doses if they were receiving 4 full doses.

The blood pressure-lowering effect of the drugs was estimated as a function of treatment dose and pre-treatment blood pressure, and was not dependent on types of drugs, except for beta blockers. Beta-blockers have been shown to be more effective than the other studied antihypertensive drugs in lowering blood pressure among patients with previous history of CVD (relative risk of 0.71, 95% confidence interval 0.66 to 0.78).[1] We included this effect in our model and found that for patients with CVD history, the MDPT tended to favor beta-blockers over other types of drugs.

The estimated effect of one drug at standard dose in lowering blood pressure from pre-treatment blood pressure P was calculated as $(9.1+0.10(P-154))$ systolic blood pressure. The estimated blood pressure reduction for higher standard dose was calculated by applying this

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equation to each drug in turn, allowing for the effect of the first in lowering pretreatment blood pressure for the second, and the second for the third, and so on. The blood pressure reductions from half standard dose were calculated as $(R+n*0.078(P-150))$ systolic blood pressure, where R is the blood pressure reduction at 150 mm Hg systolic blood pressure, n is the number of drugs, and P is the pretreatment blood pressure. Using these equations yields the following estimates of R:

Number of drugs at standard dose	R
One drug half standard dose	6.7
Two drugs half standard dose	13.3
Three drugs half standard dose	19.9
Four drugs half standard dose	26.5

Given SBP changes from blood pressure medication, the relative risk reduction for MI and stroke was estimated using previously published equations (equations (1) and (2) below).[6] The equations were estimated by fitting curves to data from a meta-analysis of prospective patient level data on blood pressure and CVD mortality.[7]

$$\text{Slope MI} = -1.1009E\text{-}05\ \text{age}^2 + 8.6305E\text{-}04\ \text{age} + 3.5176E\text{-}02 \quad (1)$$
$$\text{Relative risk of MI} = 2\text{^}(\text{change in SBP} * \text{slope MI})$$

$$\text{Slope stroke} = 2.5946E\text{-}05\ \text{age}^2 + 2.3052E\text{-}03\ \text{age} + 2.2168E\text{-}02 \quad (2)$$
$$\text{Relative risk of stroke} = 2\text{^}(\text{change in SBP} * \text{slope stroke})$$

eText 3. Risk of myocardial infarction (MI) or stroke

We used validated equations of monthly risks of MI and stroke estimated by fitting exponential curves to data on age and sex-specific incidence of first MI and stroke from the Framingham Heart Study (1948-2003), published by the National Heart, Lung, and Blood Institute.[6, 8]

Given no history of MI (x = age in years), monthly risk of MI is:

$$\text{Male: } y = 0.0001 * e^{0.0312x} \quad (3)$$
$$\text{Female: } y = 8E-06 * e^{0.0599x} \quad (4)$$

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Given no history of stroke (x = age in years), monthly risk of stroke is:

$$\text{Male: } y = 9E-06 * e^{0.0622x} \quad (5)$$

$$\text{Female: } y = 3E-06 * e^{0.0741x} \quad (6)$$

Given history of CVD, the risk of MI or stroke without a history of CVD was multiplied by a constant with a mean of 2, standard deviation 1.0204, gamma distribution (shape=3.84166, scale=0.520608).

To account for other CVD risk factors, we adopted a previously published approach in which weights are assigned to each individual based on the following risk factors used in the Framingham risk equations[9, 10]: age, total cholesterol, HDL cholesterol, hypertension treatment status, smoking, and diabetes. Individual Framingham risks were divided by the mean Framingham risk of each cohort (defined by age, sex, race, and income), then used to weight each individual's baseline MI and stroke risk equations (equations (3)-(6). The Framingham risk equations are as follows:

For males:

Individual_FHS_risk = (1-0.88936)*exp((3.06117*log(age) + 1.12370*log(total_cholesterol) + 0.93263*log(HDL_cholesterol) + 1.99881*log(SBP_treated) + 1.93303*log(SBP_untreated) + 0.65451*smoking + 0.57367*diabetes - 23.9802)

For females:

Individual_FHS_risk = (1-0.95012)*exp((2.32888*log(age) + 1.20904*log(total_cholesterol) - 0.70833*log(HDL_cholesterol) + 2.82263*log(SBP_treated) + 2.76157*log(SBP_untreated) + 0.52873*smoking + 0.69154*diabetes - 26.1931)

$$\text{Weights assigned to individual} = \frac{\text{Individual FHS risk}}{\text{Mean FHS risk of each cohort}}$$

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eText 4. Mortality after myocardial infarction (MI) or stroke

We used validated equations of age- and sex-specific risk of mortality after MI and stroke developed by fitting exponential curves to the ratio of incidence of fatal events to total incidence of events. Data on fatal MI and total incidence of MI was obtained from the Framingham Heart Study. The ratio of fatal stroke to stroke incidence was obtained from the Cardiovascular Health Study.[6, 8] This yields the following estimated mortality risks.

Risk of mortality after MI (x = age in years):

Male: $y = 0.0289 * e^{0.0269x}$

Female: $y = 0.0004 * e^{0.0706x}$

Risk of mortality after stroke (x = age in years):

Male: $y = 0.0003 * e^{0.0782x}$

Female: $y = 0.0034 * e^{0.0428x}$

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eFigure 1. Illustration of decision making process in the Markov Decision Process This figure illustrates how the MDP chooses the optimal action (treatment decision) at each decision epoch. The transition probabilities from the current state to the next are determined by which action is taken, and each transition is associated with corresponding rewards. This illustration has three actions in different colors. The numbers in each parenthesis are the transition probability and reward associated with each action. The MDP chooses an action that will maximize total rewards by calculating expected rewards from each action over the simulated horizon.

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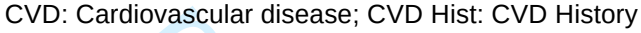
eFigure 2. Schematic of health states in the Markov Decision Process



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eFigure 3: Illustration of a single patient receiving different treatments under MDP-based treatment (MDPT) versus current guidelines. A single patient with a certain set of demographic features and CVD-related covariates is recommended for different treatment regimens. JNC8 and Intensive JNC8 recommend no treatment. MDPT recommends a half dose of beta-blocker for this patient with a blood pressure that is below the current targets due to his/her CVD-related covariates that indicate high risk of CVD.

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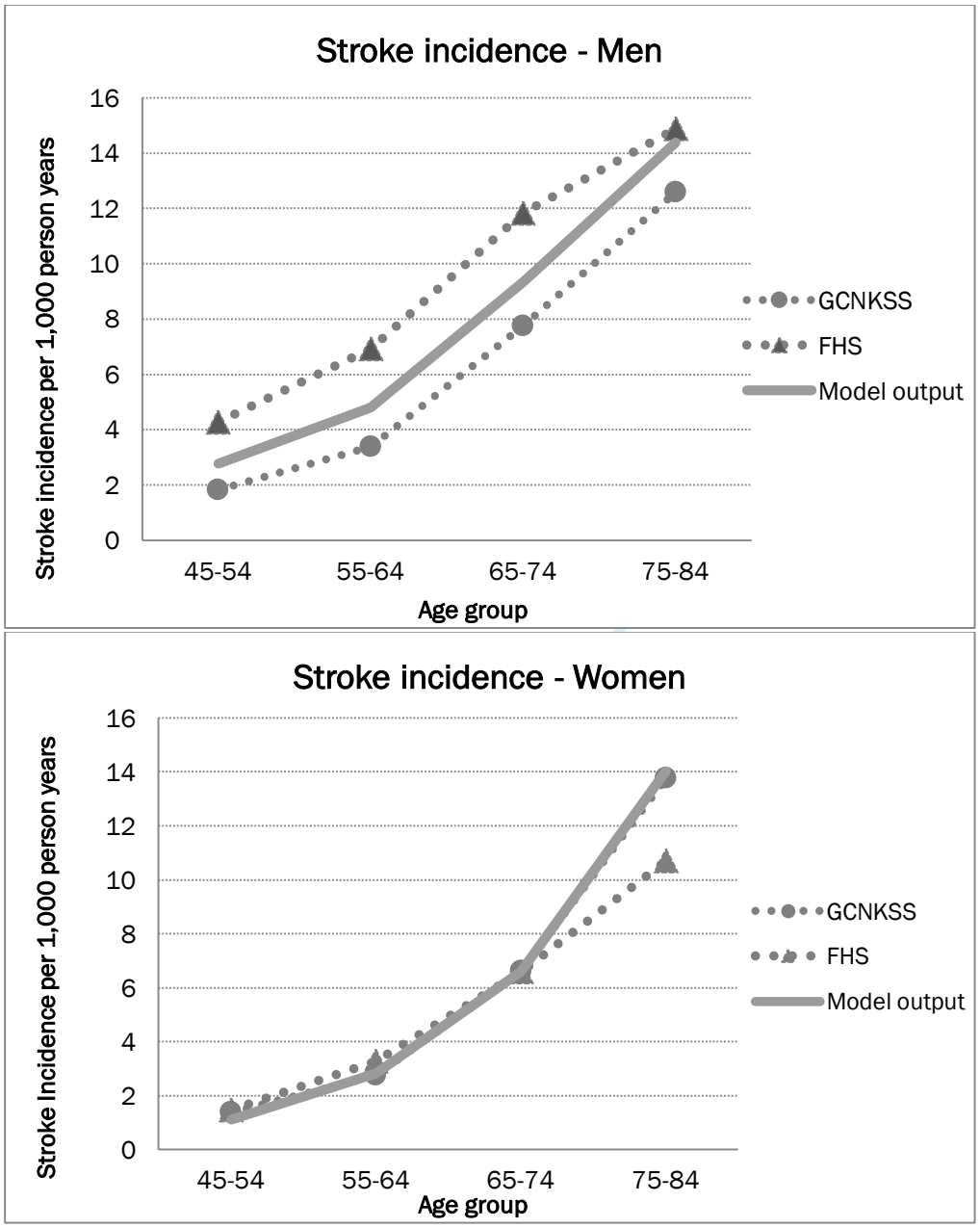
eFigure 5. Calibration results: stroke incidence We considered our targets were met if the projected incidence fell within the interval between the estimates from Framingham Heart Study (FHS) and the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS)



Appendix

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eFigure 7. QALYs in eachdisease tate overpatient lifetimes

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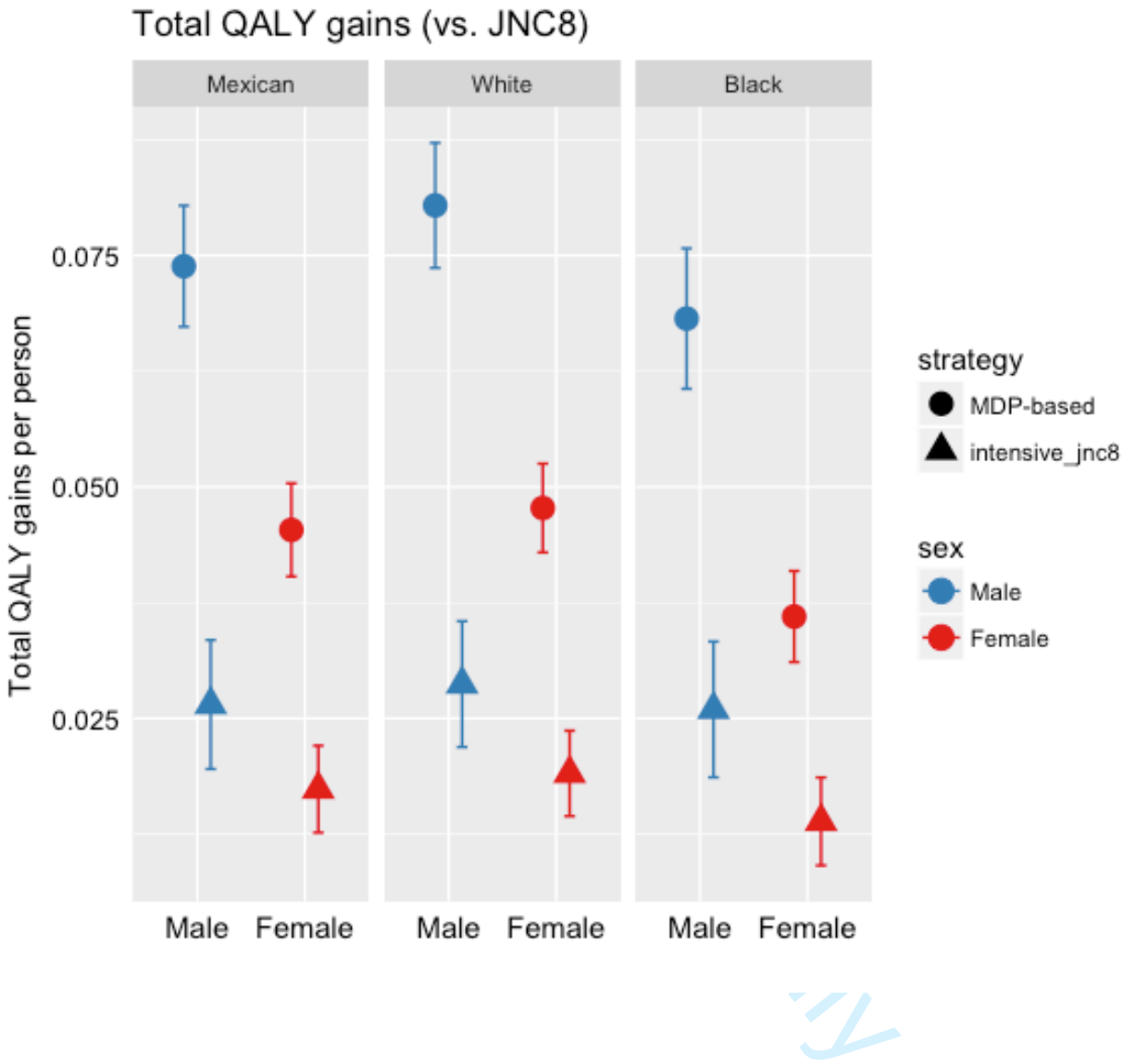
eFigure 8. Total QALY gains over patient lifetimes for the Intensive JNC8 strategy and the MDP-based treatment strategy, compared to the JNC8 strategy



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eFigure 9. Comparison of medications selected by MDP-based treatment (MDPT) approach vs. current guidelines

Without CVD History

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With CVD History

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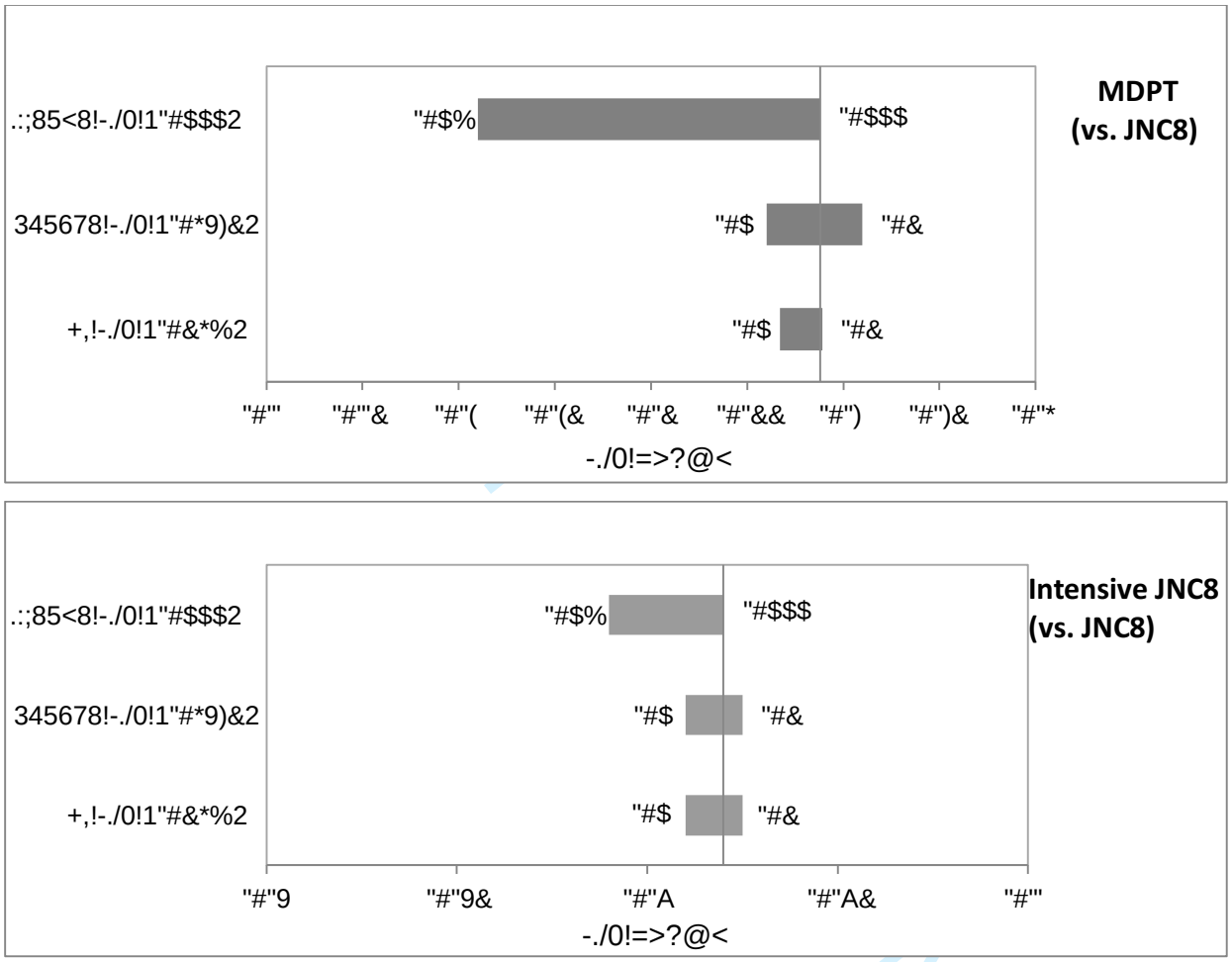
eFigure 10. Sensitivity analysis: QALY gains from the MDP-based treatment (MDPT) strategy and the Intensive JNC8 strategy (vs. JNC8). The vertical lines represent the QALY gains in the base case analysis, and the horizontal bars represent the variation of the QALY given variations of parameters. The numbers at each end of the bars represent the lower and upper bounds of the value used for each parameter.



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eFigure 11. Sensitivity analyses: Treatment dose levels for different adverse event QALY weights

Treatment side effect QALY weights (dynamic: MDP-based)

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MI QALY weights (dynamic: MDP-based)

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Stroke QALY weights (dynamic: MDP-based)

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eTable 1. Risk of Adverse Events from Medications: Percentage of Patients with One or More Symptoms Attributable to Treatment*[1]

Medication	Half dose		Standard dose		Twice standard dose	
	Mean	SD	Mean	SD	Mean	SD
ACE- I	3.9	3.88	3.9	2.24	3.9	2.09
ARB	-1.8	4.28	0	1.79	1.9	3.83
Beta-blocker	5.5	2.6	7.5	1.79	9.4	2.6
CCB	1.6	2.65	8.3	1.79	14.9	2.95
Thiazide	2	2.14	9.9	1.68	17.8	3.21

*Calculated as difference between treated and placebo groups in proportion of participants who developed one or more symptoms, excluding headaches, which were significantly less common in people receiving treatment

Note: The adverse event rates from higher doses were linearly extrapolated up to 4 standard doses.

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eTable 2. Comparison of Simulated Population and NHANES, 2003-2014

Characteristics [Mean or N (%)]	Simulated population	NHANES
Age (years)	50.52	49.20
Male	50.2 %	50.9 %
Race/ethnicity		
Mexican American	11.0%	11.5%
Non-Hispanic White	63.4%	62.9%
Non-Hispanic Black	25.4%	25.5%
MI History	4.26%	4.26%
Stroke History	3.26%	3.10%
SBP	124.1	122.7
Total cholesterol	197.1	195.0
HDL cholesterol	52.73	53.01
Smoking prevalence	21.0%	20.8%
Type 2 diabetes prevalenc	13.5%	13.1%
Kidney disease history	18.9%	22.3%
MANOVA testing	p-value: 0.4268	

R outputs

```
> summary(manova(cbind(log_sbp,log_tchol,log_hdl,smoke,
hbp_tx,diab,premi,prestroke,ckd) ~ pop, data = comb.data),test =
"Hotelling-Lawley")
              Df Hotelling-Lawley approx F num Df den Df Pr(>F)
pop            1       2.5318e-05   1.0127      9 359990 0.4268
Residuals 359998
```

Based on the outputs from MANOVA test above, it can be seen that the patient covariates are not statistically different between the simulated population and NHANES population (real population data).

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eTable 3. Quality-of-Life and Cost Estimates for Disease States and Adverse Events

By disease states and adverse events, mean (sd)

Disease states	Quality of life	Sources
MI	0.578	5, 11
Stroke	0.7165	5, 11, 12
Post CVD	0.9	5, 11
Adverse event	0.999	5

Disease states	Annual cost	Sources
MI	$44,267	12
Stroke	$23,254 (1400)	12
Post CVD	$5,208 (356)	13
Adverse event	(see below)	

Annual costs of medications and associated adverse events[12, 14]

Dose	Antihypertensive drug costs	Costs of adverse events*
0.5 standard doses	gamma(1.24, rate = 0.01)	$65.92
1.0 standard dose	gamma(1.66, rate = 0.01)	$131.40
1.5 standard doses	gamma(0.216, rate = 0.001)	$162.63
2.0 standard doses	gamma(0.238, rate = 0.001)	$193.87
2.5 standard doses	gamma(0.298, rate = 0.001)	$225.93
3.0 standard doses	gamma(0.357, rate = 0.001)	$258.05
3.5 standard doses	gamma(0.430, rate = 0.001)	$258.05
4.0 standard doses	gamma(0.496, rate = 0.001)	$258.05

* Costs of adverse events were estimated based on hospitalization costs, average cost (used for infrequent hospitalized drug-related adverse events) and high costs (used for rare hospitalized drug-related adverse events), and incidence rates of serious adverse effects of medication (common, infrequent, and rare).

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eTable 4. Comparison of MDP-based treatment (MDPT) vs. Intensive JNC8 Strategies

	Patients treated similarly by both Intensive JNC8 and MDPT strategies	Patients treated more intensively by MDPT strategy	Patients treated more intensively by Intensive JNC8 strategy
% of population	19.1	17.6	63.3
Mean initial 10-year CVD risk (%)	14.5	18.6	12.7
Mean post-10 years of treatment 10-year CVD risk (%)	14.6	14.8	14.6
QALY loss saved from CVD events, per 1000 patients treated compared to Intensive JNC8	1.85	2.17	1.25
QALY loss saved from adverse events, per 1000 patients treated compared to Intensive JNC8	0.03	-0.04	0.07
Total QALYs saved, per 1000 patients treated, compared to Intensive JNC8	43.4	46.8	31.7

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eTable 5. Baseline MI History Prevalence(%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	0.00	NA	0.72	0.25	6.92	1.04
	NH White	0.21	0.04	2.31	0.18	15.42	0.48
	NH Black	0.00	NA	4.43	0.61	12.11	0.75
Female	Mexican	0.00	NA	1.26	0.29	4.11	0.60
	NH White	1.34	0.22	1.32	0.16	8.71	0.38
	NH Black	0	NA	0	NA	5.91	0.06

eTable 6. Baseline Stroke History Prevalence(%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	0.00	NA	1.91	1.89	9.43	3.94
	NH White	0.14	0.13	0.42	0.24	6.51	1.48
	NH Black	0.00	NA	1.98	1.72	12.61	3.76
Female	Mexican	0.00	NA	1.51	8.66	2.68	2.30
	NH White	1.05	1.04	1.69	0.61	7.95	1.72
	NH Black	0.33	0.32	4.49	2.32	8.02	2.95

eTable 7. Baseline Hypertension Medication Use Prevalence(%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	1.46	1.48	9.75	5.26	41.66	8.53
	NH White	3.95	1.49	14.25	2.35	52.41	2.41
	NH Black	5.76	1.41	33.54	4.48	62.41	3.91
Female	Mexican	7.88	5.24	6.47	3.48	47.86	10.54
	NH White	0.81	0.64	24.70	3.30	54.23	3.42
	NH Black	9.48	3.41	43.57	4.95	75.36	6.23

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eTable 8. Baseline Systolic Blood Pressure (mmHg)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	121.4	1.2	124.1	3.2	135.1	7.6
	NH White	120.5	1.2	124.4	1.2	131.1	1.1
	NH Black	123.5	1.0	128.5	1.4	136.8	1.2
Female	Mexican	110.6	1.4	120.3	2.4	138.5	3.9
	NH White	109.9	0.7	121.2	1.1	135.3	1.3
	NH Black	113.8	1.3	128.5	1.9	140.4	1.9

eTable 9. Baseline Total Cholesterol (mmol/L)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	179.1	5.4	208.8	6.8	187.8	8.1
	NH White	191.5	4.4	206.4	2.1	187.8	1.4
	NH Black	182.3	3.3	190.8	5.0	184.9	4.6
Female	Mexican	187.2	5.6	208.9	6.7	208.6	9.5
	NH White	189.8	2.9	209.6	2.9	208.5	2.4
	NH Black	182.9	2.8	201.4	3.9	206.9	5.6

eTable 10. Baseline HDL Cholesterol (mmol/L)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	44.8	1.8	52.8	3.7	48.4	4.4
	NH White	47.3	1.1	49.1	0.8	51.2	0.6
	NH Black	49.5	1.5	54.9	2.7	53.0	0.7
Female	Mexican	58.7	2.4	55.7	4.1	53.3	2.4
	NH White	58.5	1.0	60.0	0.9	63.0	1.0
	NH Black	59.4	1.6	62.4	1.7	64.7	3.2

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eTable 11. Baseline Smoking Prevalence (%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	26.7	6.1	18.4	10.6	16.9	4.3
	NH White	30.9	3.1	24.1	3.6	11.9	2.8
	NH Black	27.6	4.5	35.5	6.8	22.1	5.0
Female	Mexican	9.5	4.5	26.2	9.0	9.9	3.1
	NH White	27.2	4.5	16.4	3.0	12.7	2.5
	NH Black	23.7	6.6	22.7	4.6	15.1	4.5

eTable 12. Baseline Type 2 Diabetes Prevalence (%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	0	NA	19.4	7.3	37.2	9.3
	NH White	1.3	0.7	4.9	1.3	14.7	2.2
	NH Black	5.1	1.5	14.2	5.7	32.9	5.0
Female	Mexican	2.7	1.2	5.2	2.1	30.7	4.8
	NH White	2.8	1.7	4.3	1.1	12.9	1.6
	NH Black	2.6	1.6	15.8	4.5	34.1	3.8

eTable 13. Baseline Chronic Kidney Disease (CKD) Prevalence (%)

		Age					
Sex	Race	20-39	20-39	40-59	40-59	60-85	60-85
		Mean	SE	Mean	SE	Mean	SE
Male	Mexican	10.5	3.3	2.6	2.3	19.4	5.9
	NH White	14.5	2.0	17.6	2.1	14.7	2.9
	NH Black	1.4	0.7	4.2	2.1	10.6	3.3
Female	Mexican	25.8	6.9	22.5	6.6	48.5	4.4
	NH White	23.2	4.3	41.1	2.4	42.8	3.2
	NH Black	6.9	1.7	6.8	1.8	13.6	3.4

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References

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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 No/ line No
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.	
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.	
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.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
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.	
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.	

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		11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.
	Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.
	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.
		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.
	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.
	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.
	Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.
	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.
	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.
	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.
	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

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		of methodological assumptions (such as discount rate, study perspective).	
	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.	
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.	
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.	
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.	
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.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

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

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