## Supplemental Material

**Appendix A.** Technical Appendix

Our model was in part based on an already published model.[1] Details are included in the supplemental material to that paper. This includes details of how we developed a large, representative population from the National Health and Nutrition Examination Survey (NHANES) using Monte Carlo modeling. We estimated event rates and event mortality rates from best available studies, including the AHA Annual Statistics. We estimated QALYs lost per event from best available survey data. We also calibrated the model to national data using best available data from CDC and the AHA Annual Statistics. As in the prior study, we estimated that a non-fatal MI would triple the standardized mortality rate (SMR) for a patient[2, 3] and that a non-fatal stroke would triple the SMR if the patient is under 60 years old, and double it if the patient is 60 or older.[4, 5] See Supplemental Tables 1 and 2 for data.

### Model structure

The model had 4 states – healthy, dead, stroke survivor, and coronary heart disease (CHD) survivor (see Supplemental Figure 1). All patients began the model in the "healthy" (ie, free of cardiovascular disease) state. Over the course of 5 years participants had CHD and stroke events at the rate calculated (see below) and competing non-cardiovascular mortality estimated from Centers for Disease Control and Prevention Life Tables.[12] When a participant had an event the overall QALY effect of the event was calculated (see "Estimates of utility loss"). They were otherwise censored from the study, since this was a study of primary prevention. This also means there will be no concurrent or competing events. Fatality rates per event for CHD or stroke event (the likelihood that a CHD or stroke event will be fatal) were developed from National Center for Vital Statistics Causes of Death[13] data. These results were calibrated to the estimated event rates to derive age- and sex-adjusted estimates of event fatality rates. For ease of modeling, we used a single five-year cycle and estimated events occurring on average at year 2.3, which is consistent with compounding rates. Since there is no asymmetry between time-varying covariates (ie, TTT and BTT will be affected the same ways), this is a safe assumption.

**Sample development**

We desired a nationally representative sample based on NHANES data, but one large and robust enough for precise simulation estimates. [15] As described previously,[1] to simulate a 0.1% sample of the eligible population, we first expanded the data to 417,138 participants (a 0.3% sample) by applying the NHANES sample weight to the original participants. We then we performed two simulation steps to create a more robust data set. First, we conducted a first-order Monte Carlo simulation[15] by obtaining predicted values from chained multivariate regressions and adding residuals randomly drawn from their normal distribution. Out of this sampling pool, we randomly sampled 176,000 simulated participants (0.1% sample of the eligible population) as our primary population. The size of the sample was based on estimates of the sample size needed for stable output and was later verified when repeated samples showed our results were highly stable. To account for the 4% of the population who had missing values in systolic and diastolic blood pressure in NHANES, we imputed using switching regression, an iterative multivariable regression technique.[16]

To minimize the need to estimate untreated blood pressure for those people on anti-hypertensive medications, we used NHANES III, rather than the more recent NHANES surveys. This sample had high quality data, but far fewer people were on antihypertensive medications than more recent studies. This decreases the need to estimate the untreated blood pressure within the population, creating a more accurate model.

**Estimates of blood pressure and CHD/CVD event rates.**

The most dramatic model changes in this study from the prior study examining aspirin therapy[1] were in the estimates of blood pressure. Major efforts were made to make blood pressure estimates as realistic as possible.

First, we estimated the average effect of each of four medication changes on systolic and diastolic blood pressure. Data was again obtained from the same large meta-analyses (Supplemental Table 4).[11, 17]

To simulate real-world circumstances, our study estimates accounted for both clinical uncertainty about blood pressure values in real-world practice, including measurement error and random biological variation, and patients' true variability in treatment response (based on the meta-analysis by Law and colleagues[17] and our prior work.[18, 19], see Supplemental Table 3). Each patient had two variables for their diastolic and systolic blood pressures for each simulation iteration: a 'true' value that only included variation in the patients' treatment response, and a clinical value that also included measurement error or random biological variation (based on an averaged of two blood pressure measures and including a coefficient of variation of 0.09[20]). In the base case, all clinical decisions were based on the "clinical" blood pressure value, and all estimates of the risk associated with blood pressure levels are based on the "true" blood pressure value, however, in sensitivity analyses, measurement error was varied from nonexistent (ie, the "clinical" measure and "true" measure was the same) to over twice the estimated value.

In the TTT model, treatment decisions are made on the basis of *observed* blood pressure values. Blood pressure is known to have poor test-retest reliability, with problems caused by diurnal variation, variation based on patient mood, and poor equipment creating measurement error and random variation. To account for this, observed blood pressure values included random variation due to measurement error. In sensitivity analyses, this variation was altered from no BP uncertainty up to an assumption that decisions are made on the basis of one measurement only.

In the BTT model, treatment decisions are made on the basis of *expected* event rate reductions. Expected changes can only use the patient's current observed value and the average reduction from the next medication, so all BTT estimates lack knowledge of future clinical variability in treatment response.

**Effect of blood pressure change on CHD and Stroke**

As directly as possible, we estimated the effect of blood pressure change on CHD and stroke risk from the previously cited meta-analysis.[11] The paper has a table demonstrating these relationships per decade of age, since blood pressure reduction has smaller effects on CHD and stroke rates in the elderly than in younger people. To implement this model while removing digit preferences, we used the data from this table in a regression model, with the results in Supplemental Table 4. The benefits of starting a single medication vary from a relative risk reduction of 34% for a young adult with SBP > 180 to 11% in someone over age 80 with an SBP <130. Estimates of CHD and stroke risks for people on treatment were estimated directly from the event reduction attributable to the treatment.

In the base case we established a 16% reduction in benefit for the third medication used to account for declining effects of a medication when used as the third or fourth as opposed to the first or second hypertensive treatments.[21]

**Estimates of utility loss**

The clinical effect of CHD and stroke on mortality, on QALY loss per event, and the measures of treatment disutility were estimated using previously published techniques.[3] In brief, we estimated the expected years of life remaining from NCHS Life Tables for all patients.[12] Fatal events caused a loss of one QALY for each year of life lost from the event. Non-fatal events harmed QALYs in three ways – they cause a decrease in quality of life the year of the event, a smaller decrease in quality of life every remaining year after the initial event, and a reduction in life expectancy caused by the event. Based on previous literature, a non-fatal CHD event would decrease the victim's life expectancy (ie, triple the standardized mortality ratio) for a patient[2, 3] and a nonfatal stroke event halved the victim's remaining life expectancy if the victim's age is less than 60 and by half if the victim is over 60. [4, 5] See Supplemental Tables 1 and 2 for data.

All QALY assessments were calculated with a 3% discount rate.

**Appendix B.** Illustration of the differences in management by BTT vs. TTT

To demonstrate the difference in clinical treatment by the BTT vs. TTT strategies, here we show the clinical implications of the differences between the strategies. First we describe the clinical differences, then we show how management differs in 3 illustrative example patients.

Clinically, those treated more aggressively by the TTT approach generally had higher blood pressures but lower CVD risk. Due to their higher CVD risk, men and smokers are treated more intensively in the BTT strategy than in the TTT strategy. Patients with diabetes, in spite of having a lower blood pressure goal in TTT guidelines, actually received more aggressive BP treatment on average by BTT than TTT.

In Supplemental Table 5 we show 3 hypothetical patient cases to clarify by example how the BTT approach resulted in substantially greater benefit per person treated. Patients A, B, and C are all 44 years old and have identical mildly elevated cholesterol values. Patients A and B have SBP of 144. Patient A is a woman who does not smoke. Patient B is a man who does smoke. By current guidelines they would be treated identically, each receiving a single medication. However, the smoking man (Patient B) has well over twice the CVD risk and thus receives much greater benefit from treatment. Patient C is identical to patient B except his SBP of 138 would put him below the recommended treatment threshold for current TTT guidelines, despite being much more likely to benefit than patient A. Patient A, with low benefit, would be recommended treatment by TTT but not BTT. Patient C, with high benefit but SBP below 140, would be recommended treatment by BTT but not TTT.

**Appendix C.** Effect of altering disutility on clinical benefit

The treatment disutility is the overall harm, in quality-adjusted life-years per year of treatment per medication, that a person attributes to a medication. Included in the treatment disutility is the harm due to side effects, dislike of taking the medication, and medication cost. It is an inherently subjective value, but it is one that is important to patients and should not be ignored in clinical decision-making. Furthermore, clinical disutility varies between patients.[22]

To examine this finding, we created Supplemental Figure 2. In this figure, we varied the amount of disutility attributable to one medication. We found that changing the treatment-related disutility has a large effect on overall clinical treatment benefit, but no effect on the improved efficiency of BTT over TTT. The effect of treatment disutility is most pronounced in the high risk patients who receive the most treatment. In absolute terms, these are still the patients with the largest clinical benefit, but that benefit declines as treatment disutility (and treatment intensity) increases.

**Supplemental Figure 1:** Markov state transition diagram. All participants begin in the healthy state and can progress to noncardiovascular mortality or have a cardiovascular event. Noncardiovascular mortality is defined as death by any cause other than CHD or stroke. Cardiovascular events can be fatal (defined as death in the first year) or nonfatal. Once a patient has had a nonfatal event the clinical implications are calculated, but they are removed from the model, since this is a model of primary prevention. CHD = coronary heart disease

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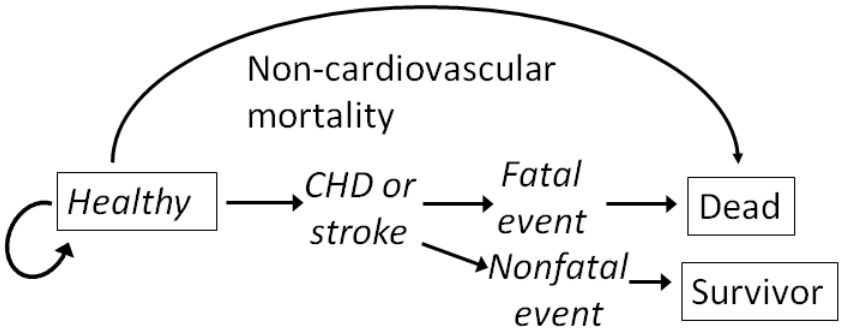
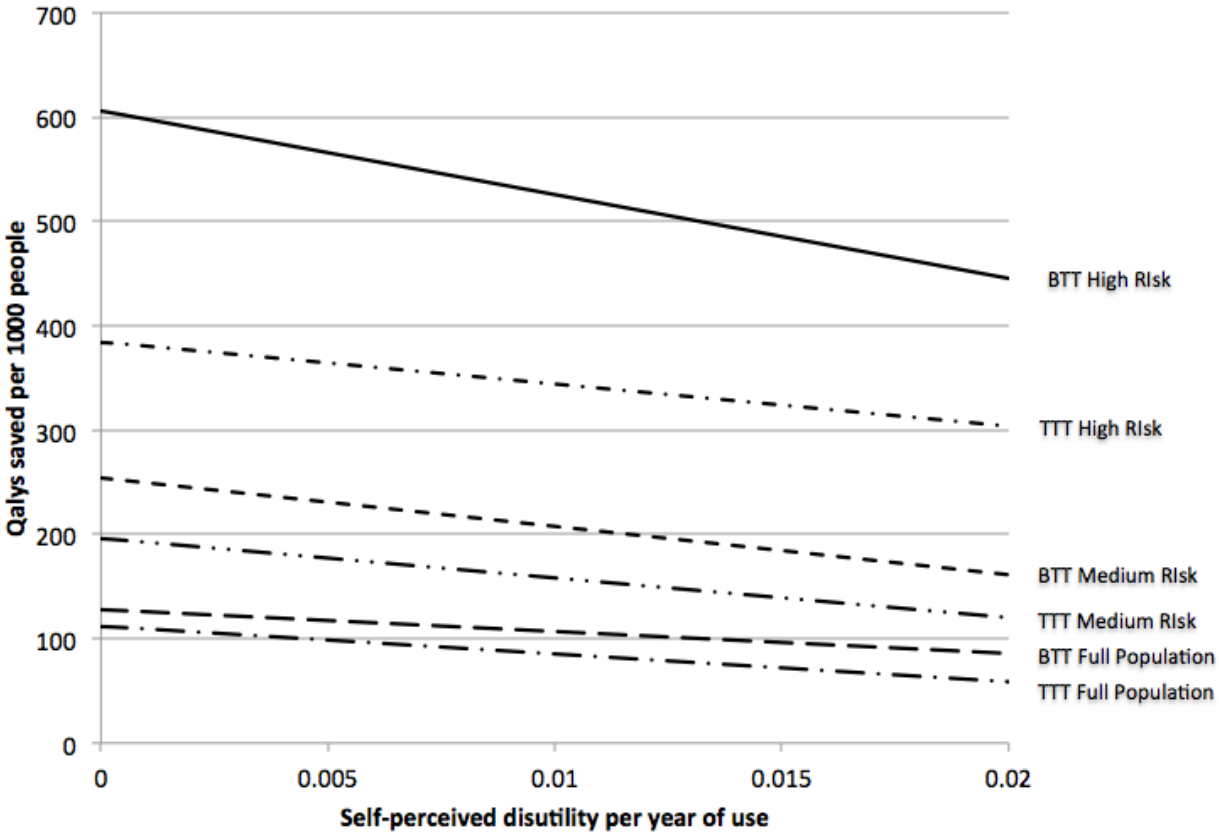


**Supplemental Figure 2. Relationship between treatment disutility and clinical treatment benefit.**[*]




Abbreviations: QALYs, quality-adjusted life-years; BTT, benefit-based tailored treatment; TTT, treat to target

[*]Medium-risk patients have 5-year event rate between 4.5% and 9%. High risk patients have 5-year event rate >9%.

**Supplemental Table 1. Model parameters for clinical effect of CVD events**

| | CHD | Stroke |
|---|---|---|
| Event rate | FHS[6] | FHS[6] |
| Event mortality rates | Derived from NCVS[3, 7] | Derived from NCVS[3, 7] |
| SMR mortality after year 1 | 2.0[2] | 3 if aged <60 years, 2 if <age 60, 2 if > age 60[2] |
| QALY loss | | |
| Year of event | 0.88[8] | 0.67[8-10] |
| Per year, afterwards | 0.90[8] | 0.90[8] |
| RRR from treatment[11*] | 0.906 – (4.12 *$RRR_{SBP*}$) + (age * 0.0015)[11] | 0.087 – (4.73 * $RRR_{SBP}$) + (age * 0.0020)[11] |

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; FHS, Framingham Heart Score; NCVS, National Center for Vital Statistics; SMR, standardized mortality rate: QALY, quality-adjusted life-year; RRR, relative risk reduction

*RRR (relative risk reduction): (Pre-treatment measurement – post-treatment measurement)/ pre-treatment measurement

**Supplemental Table 2. Fatality rate per event [12-14]**

| | CHD | | Stroke | |
|---|---|---|---|---|
| | Men | Women | Men | Women |
| 35-44 | 12 | 26 | 3 | 4 |
| 45-54 | 19 | 37 | 7 | 8 |
| 55-64 | 26 | 48 | 11 | 11 |
| 65-74 | 35 | 64 | 16 | 16 |
| >75 | 44 | 64 | 21 | 21 |

Abbreviations: CHD, coronary heart disease

**Supplemental Table 3. Values assessed for decision-making[*]**

| Value | Use | Post-treatment measurement |
|---|---|---|
| True | Outcome/benefit assessment | Pre-treatment true value - average treatment benefit + variation in treatment response |
| Observed | Treat-to-target decision-making | Pre-treatment true value - average treatment benefit + variation in treatment response + measurement error |
| Expected | Benefit-based tailored treatment decision-making | Pre-treatment observed value – average treatment benefit |

[*]For each medication step, we calculated the true, observed, and expected values for systolic blood pressure, diastolic blood pressure, coronary heart disease risk, and cardiovascular disease risk. Each measure had a specific use in the model

**Supplemental Table 4. Effect of blood pressure change on CHD and stroke relative risk reduction (RRR)[*11]**

| | RRR for 60-year-old receiving one medication | beta | Per percent change in mmHg SBP | Per year of age |
|---|---|---|---|---|
| CHD RRR | 0.25 | 0.906 | -0.0412 | 0.0015 |
| Stroke RRR | 0.29 | 0.87 | -0.0473 | 0.0020 |

Abbreviations: CHD, coronary heart disease; RRR, relative risk reduction

[*]This parameter uses the data from the cited meta-analysis to estimate the effect of medical blood pressure reduction on CHD and stroke relative risk reduction. The results are identical to table 3 in that paper except the linear model removes digit preference and were developed from a simple multivariate regression from their data ($r^2$>0.95). For a given change in blood pressure, people with higher blood pressures have slightly smaller relative risk reduction and older people have slightly larger RRR.

**Supplemental Table 5. Example patients**[a]

| Example patient | FHS 5-year CVD rate (%) | Absolute CVD risk reduction of 1 medication | Is medication recommended by | |
|---|---|---|---|---|
| | | | TTT | BTT |
| A: 44y.o. woman, nonsmoker, SBP 144 | 2.1 | 0.10 | Yes | No |
| B: 44y.o. man, smoker, SBP 144 | 5.8 | 0.23 | Yes | Yes |
| C: 44y.o. man, smoker, SBP 138 | 5.4 | 0.21 | No | Yes |

Abbreviations: HDL, high-density lipoprotein cholesterol; FHS, Framingham Heart Score; CVD, cardiovascular disease; TTT, treat-to-target; BTT, benefit-based tailored treatment; y.o., year old; SBP, systolic blood pressure

[a]All patients have total cholesterol = 210, HDL cholesterol = 35, and none has diabetes.

**Supplemental Works Cited**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