Using Benefit-Based Tailored Treatment to Improve the Use of Antihypertensive Medications

Jeremy Sussman, MD, MS; Sandeep Vijan, MD, MS; Rod Hayward, MD

Background—Current guidelines for prescribing antihypertensive medications focus on reaching specific blood pressure targets. We sought to determine whether antihypertensive medications could be used more effectively by a treatment strategy based on tailored estimates of cardiovascular disease events prevented.

Methods and Results—We developed a nationally representative sample of American adults aged 30 to 85 years with no history of myocardial infarction, stroke, or severe congestive heart failure using the National Health and Nutrition Examination Survey III. We then created a simulation model to estimate the effects of 5 years of treatment with treat-to-target (treatment to specific blood pressure goals) and benefit-based tailored treatment (treatment based on estimated cardiovascular disease event reduction) approaches to antihypertensive medication management. All effect size estimates were derived directly from meta-analyses of randomized trials. We found that 55% of the overall population of 176 million Americans would be treated identically under the 2 treatment approaches. Benefit-based tailored treatment would prevent 900,000 more cardiovascular disease events and save 2.8 million more quality-adjusted life-years, despite using 6% fewer medications over 5 years. In the 45% of the population treated differently by the strategies, benefit-based tailored treatment would save 159 quality-adjusted life-years per 1000 treated versus 74 quality-adjusted life-years per 1000 treated by the treat-to-target approach. The findings were robust to sensitivity analyses.

Conclusions—We found that benefit-based tailored treatment was both more effective and required less antihypertensive medication than current guidelines based on treating to specific blood pressure goals. (Circulation. 2013;128;2309-2317.)

Key Words: epidemiology ■ hypertension ■ primary prevention ■ treatment outcome

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decision making, but even these guidelines emphasize treating to a prespecified BP value rather than basing decisions directly on estimates of CVD event reduction.

Here, we examine whether a BTT strategy for hypertension would prove superior to a traditional TTT strategy for hypertension treatment. We constructed a probability model, based on the best available evidence, to examine how many CVD events would be prevented and how many quality-adjusted life years (QALYs) would be saved with each of the 2 treatment strategies. We also assessed the implications of these strategies for individual patients and across a wide range of data assumptions.

**Methods**

**Overview**

We constructed a large simulated population with the distribution of CVD risk factors observed in the United States, derived from the nationally representative National Health and Nutrition Examination Survey (NHANES) III. We then estimated event rates of coronary heart disease (CHD) and stroke (RiskUnRx) using the Framingham Heart Study score and derived the effects of hypertension treatments (RRRx and HarmRx) from a large meta-analysis of randomized controlled trials. We chose the Framingham Heart Study score because it is the most established, validated, and commonly used. We then developed a Markov simulation model that compared a BTT strategy with a JNC-style TTT strategy. The model estimates the impact of each BP treatment strategy on CVD events and QALYs for each patient in the simulated population. This approach to using the best available evidence to estimate the population and individual net benefits to different treatment strategies has been used and described previously.

We then estimated the lifetime effects of following the best available evidence, to examine how many CVD events and QALYs would be prevented over a lifetime. We modeled the costs of each strategy, and the population-level and individual-level outcomes were estimated from the model.

We restricted our analyses to persons aged 30 to 85 years with no history of a myocardial infarction, stroke, or congestive heart failure (ie, primary prevention) because estimates of the Framingham Heart Study score are most accurate in this population, and few individuals outside of this age range have been included in clinical trials. We created a large, robust simulated population of 167,000 people (0.1% of the eligible US population) using the method of imputation of chained equations. This technique accounts for the observed risk factor distributions, correlations, and survey weights of in the 8291 eligible participants in NHANES. As in traditional survey weighting, these 167,000 people represent the 167 million people who meet the eligibility criteria nationwide. The imputation technique ensures that the benefits of survey weighting are retained while providing a more robust representative database.

To effectively assess the benefit of different BP strategies, we estimated the untreated BP of every person in the cohort. To do that, we used the measured BP and average effectiveness of BP medications to back out estimated untreated BP for each individual, to account for the variability in BP treatment response.

**Effect of Treatment on BP and Cardiovascular Risk**

We separately assessed each patient’s untreated 5-year risk of CVD, including CHD and stroke, using equations from the Framingham Heart Study. We chose these particular Framingham models because they permit separate evaluations of CHD and stroke and include patients with and without diabetes mellitus. This is necessary because each medication reduces the risk of CHD and stroke by different amounts.

We then used data from a large meta-analysis by Law and colleagues to estimate the expected BP reduction and relative and absolute reduction in CHD and stroke risk for each of 4 possible treatment steps of increasing treatment intensity for each individual (Table 1). This meta-analysis produced estimates for treatments for systolic and diastolic BP by pretreatment BP and for CHD and stroke rates by CHD and stroke risk as well. The 4 treatment steps represent each of the 4 common, well-studied BP classes (thiazides, angiotensin converting enzymes, β-blockers, and calcium channel blockers) used in the order recommended in the JNC7 guidelines, but the medication order was varied in sensitivity analyses. We used a single standard dose for each medication to simplify presentation and because these studies showed that dosage adjustment has only small effects on outcomes. CHD risks for people undergoing BP treatment were developed from this meta-analysis by use of a multifactorial model of pretreatment risk, age, and pretreatment systolic BP (online Data Supplement).

To simulate more realistic clinical circumstances, we created values for BP and CHD and stroke risk that accounted for clinical BP measurement uncertainty and variability in treatment response. Clinical BP measurement uncertainty results from daily variations in an individual’s BP, inconsistent measurement equipment or technique, and random measurement error. Parameters for these estimations were obtained from published data. Variability in treatment response

<table>
<thead>
<tr>
<th>Table 1. Effect of Treatments on Blood Pressure</th>
</tr>
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<tbody>
<tr>
<td>Treatment Class and Order of Use</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Thiazide</td>
</tr>
<tr>
<td>ACEI</td>
</tr>
<tr>
<td>BBL</td>
</tr>
<tr>
<td>CCB</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; BBL, β-blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*Based on meta-analysis by Law et al. The low dose was used only in the sensitivity analysis.
represents true variation in BP reduction from each treatment, caused by patient biological variability, and also was derived from published data.\textsuperscript{13–15} All treatment decisions were based on the observed BP (ie, a clinic BP), which includes measurement uncertainty and true variation in response, but all estimates of treatment benefit are based on the patient’s true BP, which is known by the model but not the treating provider. These variations are fully described in the Appendix in the online-only Data Supplement; the implications of varying these factors (such as improving clinical BP measurement) were examined in sensitivity analyses. For the base case, we selected what Law et al\textsuperscript{13} call a standard dose, but in sensitivity analyses, we examined lower dosages for each medication.

Other sequelae of CVD were not included in the model because they would be very unlikely to alter the results, for multiple reasons. First, CHD and stroke are the cause of >80\% of hypertension-related QALY loss in developed countries.\textsuperscript{2} Second, most of the other sequelae of hypertension have risk factors that closely parallel CHD and stroke, including congestive heart failure,\textsuperscript{23} claudication,\textsuperscript{23} and chronic kidney disease.\textsuperscript{2} Third, the role of hypertension treatment in preventing these conditions is much less clearly estimated from current trials.

### TTT and BTT Strategies

The number of medications each patient received for each treatment strategy was determined sequentially so that the posttreatment observed BP and CVD risk were reassessed after each treatment step. The base case TTT strategy was based on JNC 7 guidelines (Figure 1).\textsuperscript{10} In this strategy, a patient’s treatment was advanced with a new BP medication if his or her observed BP was ≥140/90 mm Hg or ≥130/85 mm Hg for patients with diabetes mellitus. Medications were added sequentially until the target BP was reached or until the patient was taking 4 medications.

In the BTT strategy, treatment was advanced to the next step of therapy in 2 circumstances. First, treatment was advanced in any patient whose observed systolic BP was >150 mm Hg. This was selected because adverse effects from BP can multiply even as an isolated risk factor at very high levels and because elevations to this degree are less likely to be false-positive measurements. Second, treatment was advanced in any patient whose rate of CVD events would be predicted to decrease by a >1.7\% chance of event averted for 5 years of therapy. By this standard, patients receive a medication if it has a sufficiently high likelihood of preventing a CVD event. This threshold was chosen empirically because it leads to roughly the same number of patients being treated as does the TTT strategy, which facilitates direct comparison (see Discussion for comments on setting optimal BTT thresholds).

### Assessing the Clinical Benefits of Treatment

Using these treatment strategies, the population was then assessed in a Markov model. Each patient began in the healthy state. During the 5 years of follow-up, they could develop CVD. CVD could constitute CHD or stroke and could be fatal or nonfatal. For each patient, we estimated the clinical implications of each strategy (TTT versus BTT) on patient systolic and diastolic BP, event rates for CHD and stroke, including congestive heart failure,\textsuperscript{23} claudication,\textsuperscript{23} and chronic kidney disease.\textsuperscript{2}

## Analysis

The primary analysis compared the effects of a TTT strategy with those of BTT. These were evaluated for the clinical implications of each strategy, including an examination of who would receive treatment by each strategy and the implications on the entire population. We then specifically focused on the marginal patients\textsuperscript{8} (those patients who are treated substantially differently by one guideline versus another) to examine how many were treated differently and what the clinical implications were of that treatment difference. Multiple sensitivity analyses were performed to assess the reliability of these outcomes (Table 2).\textsuperscript{29–32}
Incremental (Marginal) Benefits of TTT Versus BTT

Approximately 97 million people (55% of the total population) would be recommended the same medications by either of the competing strategies, with 82 million of these people (46% of the total population) not being treated under either strategy. With so many people being treated similarly, the most informative analysis is to examine the differential benefits in the estimated 45% (79.9 million people) who would be treated differently under the 2 strategies (Table 4). A total of 26.5% of the total population (46.8 million people) would be treated more intensively with TTT than BTT; for these people, TTT would recommend an additional 1.9 medications per person and would save 204 QALYs per 1000 treated more intensively for 5 years. In contrast, the 18.7% of the population (33.0 million people) treated more intensively with BTT than TTT would receive an additional 2.5 medications per person and would save 487 more QALYs per 1000 people treated more intensively, more than twice the benefit as those treated more intensively by TTT (Table 4). Because BTT is based on overall cardiovascular risk, people with more risk factors, especially older men who smoke, would be treated more intensively with BTT. In contrast, people with only high BP but who have low overall cardiovascular risk would be treated more intensively with TTT.

As shown in Figure 2, people for whom similar therapy was recommended by both strategies and those for whom more...
intensive treatment by BTT than TTT was recommended received roughly twice the benefit as those for whom more intensive treatment by TTT was recommended (Figure 2; Table 4). To provide concrete examples of the clinical implications of treatment with BTT versus TTT, 3 sample patients are described in the online-only Data Supplement (Appendix II and Table V in the online-only Data Supplement).

**Sensitivity Analyses**

Multiple sensitivity analyses were performed on a wide array of parameters in the model (Table 5). A change in model assumptions had some effect on treatment intensity (ie, how many medications individuals were recommended), although BTT almost always led to fewer people being treated at the population level. BTT always had a substantially larger total population benefit. The relative benefit of BTT versus TTT per medication used was insensitive to variations in model assumptions. The most dramatic change was that BTT had an even larger relative benefit at higher levels of treatment disutility (the amount that a patient dislikes taking a medication, which includes costs, patient dislike of taking medications, side effects, and adverse events), because fewer people would be treated and thus experience treatment burdens (Figure II in the online-only Data Supplement). Improving the accuracy of BP measurement only resulted in a modest improvement in the efficiency of a TTT strategy. Similarly, assumptions that would lead to greater treatment by the TTT strategy, such as the creation of a high-risk group based around cardiac risk (such as currently exists in cholesterol guidelines) and an assumption that people would use low doses of BP medications (which is recommended in the United Kingdom), did not substantially increase the efficiency of TTT (Table 5). Altering the order in which BP medications were used also did not substantially change our results. Even changing an assumption that substantially reduced the absolute benefit of treatment,

| Table 4. Comparison of Incremental Gains of the Intensive TTT Approach Versus the BTT Approach in 177 Million US Patients |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| People Treated Identically by Both Strategies | People Treated More Intensively by TTT | People Treated More Intensively by BTT |
| Proportion treated, % (million n) | 54.8 (96.8) | 26.5 (46.8) | 18.7 (33.0) |
| Age, y | 52.0 | 55.8 | 68.8 |
| Women, % | 63 | 63 | 19 |
| Tobacco use, % | 24 | 18 | 39 |
| Diabetes mellitus, % | 5 | 8 | 13 |
| Mean initial SBP, mm Hg | 124.1 | 141.6 | 140.4 |
| Mean initial DBP, mm Hg | 74.2 | 84.6 | 76.2 |
| Mean final SBP, mm Hg | 119.6 | 120.4 | 118.3 |
| Mean final 5-y CVD risk, % | 2.6 | 2.7 | 9.5 |
| Mean final 5-y CVD risk, % | 1.9 | 1.4 | 4.3 |
| CVD events prevented, per 1000 treated more intensively | 12.2 | 22.5 | 74.7 |
| QALYs saved, per 1000 treated more intensively | 62 | 74 | 159 |
| Events prevented per medication used, per 1000 persons treated more intensively | 77.9 | 204 | 486 |

BTT indicates benefit-based tailored treatment; CVD, cardiovascular disease; DBP, diastolic blood pressure; QALYs, quality-adjusted life-years; SBP, systolic blood pressure; and TTT, treat-to-target approach.

*A patient was considered to be treated more intensively if treatment by that strategy would lead to more blood pressure medications being used.

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**Figure 2.** Average benefit per recommended medication. 
*Circle sizes are proportionate to the number of people who meet that criterion. For example, for the identical treatment group, 81.8 million people (largest green circle) would receive no blood pressure treatment with either the benefit-based tailored treatment or the treat-to-target strategy, and 3.6 million people (smallest green circle) would receive 3 blood pressure medications using either strategy. 
*At each level of treatment, people who follow the treat-to-target method saves approximately half as many quality-adjusted life-years (QALYs) as those recommended that level of treatment by benefit-based tailored treatment only or by both methods.
Table 5. Sensitivity Analyses of BTT Versus TTT*

<table>
<thead>
<tr>
<th>Treatment Intensity (BTT/TTT Ratio of Medications Used per 100 People)</th>
<th>Total Population Benefit (BTT/TTT of QALYs Saved per 1000 Treated)</th>
<th>Treatment Efficiency, (BTT/TTT of QALYs Saved per 1000 Treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.94</td>
<td>1.15</td>
</tr>
<tr>
<td>True variation in medication response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.91</td>
<td>1.12</td>
</tr>
<tr>
<td>Large: Same size as treatment response</td>
<td>0.98</td>
<td>1.19</td>
</tr>
<tr>
<td>Treatment-related disutility (0 and 0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.94</td>
<td>1.14</td>
</tr>
<tr>
<td>High (0.02 QALYs per medication per year)</td>
<td>0.94</td>
<td>1.46</td>
</tr>
<tr>
<td>Double if age ≥70 y</td>
<td>0.94</td>
<td>1.15</td>
</tr>
<tr>
<td>High risk treatments: Goal BP &lt;130/80 mm Hg if Diabetes mellitus or 10-year CVD risk &gt;20%</td>
<td>0.86</td>
<td>1.04</td>
</tr>
<tr>
<td>No circumstances</td>
<td>1.01</td>
<td>1.24</td>
</tr>
<tr>
<td>Decline in treatment benefit for additional medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No decline for additional medications</td>
<td>0.91</td>
<td>1.12</td>
</tr>
<tr>
<td>16% Decline per medication</td>
<td>1.01</td>
<td>1.21</td>
</tr>
<tr>
<td>40% Nonadherence</td>
<td>0.84</td>
<td>1.15</td>
</tr>
<tr>
<td>Low-dose BP medications (per Law et al)</td>
<td>0.79</td>
<td>1.02</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; BTT, benefit-based tailored treatment; CVD, cardiovascular disease; QALYs, quality-adjusted life-years; and TTT, treat-to-target approach.

*All values are BTT/TTT ratios. For example, the first column shows that in most circumstances, treatment is more intense by TTT; the second column shows that in all circumstances, net population benefit is greater with BTT; and third column shows that in all circumstances, treatment is more efficient with BTT.

such as assuming a 40% treatment nonadherence (we assumed 100% adherence in the base estimates), did not substantially alter the relative benefit of BTT over TTT.

**Discussion**

Clinicians and policy makers have long recognized that BP is not the only predictor of treatment benefit from antihypertensive medications. The larger absolute benefit in patients at high risk (eg, those with CVD or diabetes mellitus) has led to lower BP targets in these highest-risk patients.34,35 The present findings suggest there could be major benefit in taking an additional step in this progression: To base BP management decisions on estimates of individual-patient benefit, instead of focusing primarily on treatment based only on the intermediate risk factor of BP.

In the present study, we found that tailoring hypertension management by estimating an individual’s expected net benefit from additional BP treatment (BTT) has the potential to be a more efficient and effective strategy for improving patient outcomes than current TTT guidelines. We have also shown that net benefit can be estimated appropriately with a patient’s untreated CVD risk, BP, and current treatment regimen. The important finding in the present study is not simply that the BTT approach was better than the TTT approach, because that is true almost by definition, but that just as we found in past research on lipid therapy,8 BTT was much better. For lipid therapy, we found that BTT saved >3 times more QALYs than TTT in those treated differently by the 2 approaches, and in the present study, we found that BTT produced approximately twice as much benefit for those treated differentially for BP management.

We see BTT as a natural evolution of CVD prevention guidelines, not a divergence from them. Recent guidelines have recognized that people with elevated risk, such as those with a history of CVD or diabetes mellitus, are much more likely to benefit from treatment than those with lower CVD risk. TTT guidelines begin to account for this by recommending a lower BP goal in those at high risk,34,36 and the results of the present study suggest that BTT can further improve treatment effectiveness and efficiency and prevent many more CVD events by considering all the patient and treatment factors that clinical trials have found to influence absolute risk reduction.

The present findings are consistent with our prior work examining a BTT approach.1,6,14,15 Our group has already demonstrated how baseline risk, and not low-density lipoprotein cholesterol concentration, is central to decisions regarding statin use8 and how concentrating on overall microvascular and macrovascular risk can improve decision making over current guidelines for diabetes mellitus treatments.14,15 The present findings are consistent with another study that found that model-based hypertensive management could be more cost-effective than current care.37 Unlike that study, however, the present work considered the adverse effects of BP treatments, used a model that can be inspected directly by other researchers, and demonstrated that purchase and use of a proprietary product was not necessarily required to achieve the benefit of BTT.

The primary limitation of the main conclusion of the present study, that BTT has higher efficacy than a TTT approach, is that we are limited by the current evidence in the medical literature. Caution is always advisable when interpreting simulation models, because a model is only as good as its inputs and assumptions; however, the present study is based on very strong evidence. Most of the key parameters were drawn directly from a large meta-analysis of randomized trials,13 and...
the present study population was derived from a nationally representative sample of the US population.

Furthermore, we made several assumptions that were favorable to a TTT approach. First, the real-world accuracy of BP measurement is lower than that seen in the studies we used. Second, we assumed that the benefits of antihypertensive medications were directly related to their impact on an individual’s resting BP, rather than other effects of the medications themselves, including patient’s BP levels when active. Third, we used a very small treatment disutility, which our sensitivity analyses found greatly favored a TTT approach. Finally, improved CVD risk prevention can make BTT even more valuable. For example, if new risk prediction tools (such as the Reynolds score or coronary artery calcium score) improve our ability to risk-stratify patients beyond the Framingham score, the benefit of BTT over TTT would become even larger.

We did not include a systolic BP or diastolic BP at which further treatment was contraindicated for either strategy because the possible clinical harms of treatment toward low BP are unclear. We do believe that caution about overtreatment in older patients is particularly important. One advantage of a BTT approach is that it can easily incorporate stopping rules and any other complex assumptions or new research findings. Such modifications and updates simply need to be added to the risk-benefit estimations. We used a 5-year treatment window because longer time frames are inconsistent with appropriate clinical decision making, in that reevaluation of the need for BP treatment should occur at least every 3 to 5 years. Furthermore, the use of a 5-year window, as opposed to a lifetime window, would only alter the relative benefits of BTT versus TTT if there were delayed benefits from earlier initiation of BP treatment. We found no evidence that this occurs for BPs in the range evaluated in the present study (ie, systolic BP <150 mm Hg).

The present study demonstrates that when high-quality evidence is available, simulation models can help make the results of randomized trials more useful clinically. Although a trial directly comparing BTT versus TTT would take many years to conduct and may prove prohibitively expensive, the simulation approach used in the present study merely interprets the best available data, mainly using the results of randomized controlled trials. Of note, the BTT approach examined in the present study uses results of trials more directly than current TTT guidelines, which make many more untested assumptions, such as assuming that an individual’s degree of BP reduction as measured in routine clinical practice is accurate and that treatment disutilities are negligible.

The present study shows that BTT is more efficient than current guidelines. In the present report, we chose a benefit cut point (the 1.7% absolute event reduction per year above which we would recommend treatment) so that population-level treatment would be comparable between BTT and TTT, ensuring a clearer comparison to current TTT guidelines. We are not making global recommendations about how intensive treatment should be. It is reasonable to assume that individual patients will have different thresholds at which they would consider treatment beneficial, so that a shared decision-making approach should be adopted. More development of tools and clinical policy to support this approach is necessary.

This work also is not relevant to the importance of nonmedical prevention of CVD. For example, the value of smoking cessation likely outweighs all of these decisions, and effective changes to diet and exercise change risk factors and therefore estimated benefit.

The present study is a proof of principle that BTT could prevent more CVD events than current TTT guidelines; however, one practical limitation of our strategy’s potential effectiveness is that clinicians cannot be expected to perform the necessary algebraic calculations in their head. The model can, however, be easily placed on a computer, Web site, or handheld device and could potentially be integrated with a facility’s electronic health record, which would limit the need for data entry. With appropriate tools, this could be time efficient and quite simple.

Although technically fairly easy, widespread adoption of a BTT approach will most likely require the support of guideline organizations, changes in quality measures, and the development of easy-to-use decision support tools (preferably based on electronic health records). Although ambitious, similar changes are already occurring in the treatment of hypercholesterolemia, for which the American College of Cardiology/American Heart Association guidelines for treatment of patients with stable ischemic heart disease has recently removed its TTT component, the Veterans Health Administration system has changed its quality measures to be consistent with BTT, and treatment decision support systems (although not BTT based) already exist.

Before creating a public access decision tool for BTT, we believe it is appropriate to await public vetting of the present findings and perhaps await changes in formal guidelines and quality measures. Implementation of this work would be a major challenge, but given the importance of BP treatment, we believe such discussions should be made a priority. In the interim, even a qualitative understanding that clinicians should pay more attention to overall CVD risk when making BP treatment decisions is important and valuable.

In summary, the results of the present study suggest that CVD events can be prevented more effectively with a more comprehensive accounting for all available factors that contribute to net patient benefit, such as other clinical risk factors and polypharmacy, rather than by chiefly basing decisions on whether the observed BP level is above or below a prespecified BP target. The next wave of clinical treatment strategies may be more efficient, effective, and transparent, with a full assessment of risk and benefit and the use of BTT.

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Disclosures

None.

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The purpose of prescribing blood pressure therapy is not to treat blood pressure per se but to reduce cardiovascular disease morbidity and mortality. Most current blood pressure guidelines advocate titrating treatment towards a blood pressure goal, but many factors beyond blood pressure influence a patient’s benefit from starting and advancing blood pressure medications, especially the patient’s overall cardiovascular disease risk (as determined by risk factors including age, smoking, and lipid levels) and the medication’s relative risk reduction. In the present study, we conducted a simulation using the best available clinical evidence and compared current guidelines, which focus on achieving blood pressure goals, to a benefit-based tailored treatment strategy, which bases treatment decisions on an individual patient’s expected net absolute benefit from advancing treatment. The study found that 55% of the 176 million adult Americans aged 30 to 80 years would be treated identically under the 2 treatment approaches. For the 45% treated differently by the 2 strategies, benefit-based tailored treatment was estimated to prevent 900,000 more cardiovascular disease events over a 5-year period, saving an estimated 2.8 million more quality-adjusted life-years than conventional guidelines, despite using 6% fewer medications. Results were robust to varying assumptions across a wide range. This study suggests that making more individualized blood pressure treatment decisions based on a patient’s overall cardiovascular disease risk and the estimated benefits of advancing treatment is substantially more effective than current guidelines that emphasize treating to specific blood pressure goals.
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Supplemental Material

Appendix A. Technical Appendix

Our model was in part based on an already published model. 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 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. 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. 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 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.\textsuperscript{15} As described previously,\textsuperscript{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\textsuperscript{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.\textsuperscript{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\textsuperscript{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).\textsuperscript{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\textsuperscript{17} and our prior work.\textsuperscript{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\textsuperscript{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. 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.

**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. In brief, we estimated the expected years of life remaining from NCHS Life Tables for all patients. 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 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. 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.\textsuperscript{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.
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

<table>
<thead>
<tr>
<th></th>
<th>CHD</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Event rate</strong></td>
<td>FHS$^6$</td>
<td>FHS$^6$</td>
</tr>
<tr>
<td><strong>Event mortality rates</strong></td>
<td>Derived from NCVS$^{3,7}$</td>
<td>Derived from NCVS$^{3,7}$</td>
</tr>
<tr>
<td><strong>SMR mortality after year 1</strong></td>
<td>2.0$^2$</td>
<td>3 if aged &lt;60 years, 2 if &lt; age 60, 2 if &gt; age 60$^2$</td>
</tr>
<tr>
<td><strong>QALY loss</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year of event</td>
<td>0.88$^8$</td>
<td>0.67$^{8-10}$</td>
</tr>
<tr>
<td>Per year, afterwards</td>
<td>0.90$^8$</td>
<td>0.90$^8$</td>
</tr>
<tr>
<td>RRR from treatment$^{11*}$</td>
<td>$0.906 - (4.12 \times \text{RRR}_{SBP}) + (\text{age} \times 0.0015)^{11}$</td>
<td>$0.087 - (4.73 \times \text{RRR}_{SBP}) + (\text{age} \times 0.0020)^{11}$</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>CHD</th>
<th></th>
<th>Stroke</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>35-44</td>
<td>12</td>
<td>26</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45-54</td>
<td>19</td>
<td>37</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>55-64</td>
<td>26</td>
<td>48</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>65-74</td>
<td>35</td>
<td>64</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>&gt;75</td>
<td>44</td>
<td>64</td>
<td>21</td>
<td>21</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease
Supplemental Table 3. Values assessed for decision-making*

<table>
<thead>
<tr>
<th>Value</th>
<th>Use</th>
<th>Post-treatment measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>True</td>
<td>Outcome/benefit assessment</td>
<td>Pre-treatment true value - average treatment benefit + variation in treatment response</td>
</tr>
<tr>
<td>Observed</td>
<td>Treat-to-target decision-making</td>
<td>Pre-treatment true value - average treatment benefit + variation in treatment response + measurement error</td>
</tr>
<tr>
<td>Expected</td>
<td>Benefit-based tailored treatment decision-making</td>
<td>Pre-treatment observed value – average treatment benefit</td>
</tr>
</tbody>
</table>

*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)**

<table>
<thead>
<tr>
<th></th>
<th>RRR for 60-year-old receiving one medication</th>
<th>beta</th>
<th>Per percent change in mmHg SBP</th>
<th>Per year of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD RRR</td>
<td>0.25</td>
<td>0.906</td>
<td>-0.0412</td>
<td>0.0015</td>
</tr>
<tr>
<td>Stroke RRR</td>
<td>0.29</td>
<td>0.87</td>
<td>-0.0473</td>
<td>0.0020</td>
</tr>
</tbody>
</table>

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\textsuperscript{a}

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

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

\textsuperscript{a}All patients have total cholesterol = 210, HDL cholesterol = 35, and none has diabetes.
Supplemental Works Cited


