Personalizing the Intensity of Blood Pressure Control
Modeling the Heterogeneity of Risks and Benefits From SPRINT (Systolic Blood Pressure Intervention Trial)

Krishna K. Patel, MD; Suzanne V. Arnold, MD, MHA; Paul S. Chan, MD, MSc; Yuanyuan Tang, PhD, Yashashwi Pokharel, MD, MSCR; Philip G. Jones, MS; John A. Spertus, MD MPH

Background—In SPRINT (Systolic Blood Pressure Intervention Trial), patients with hypertension and high cardiovascular risk treated with intensive blood pressure (BP) control (<120 mm Hg) had fewer major adverse cardiovascular events (MACE) and deaths but higher rates of treatment-related serious adverse events (SAE) than patients randomized to standard BP control (<140 mm Hg). However, the degree of benefit or harm for an individual patient could vary because of heterogeneity in treatment effect.

Methods and Results—Using patient-level data from 9361 randomized patients in SPRINT, we developed models to predict risk for MACE or death and treatment-related SAE to allow for individualized BP treatment goals based on each patient’s projected risk and benefit of intensive versus standard BP control. Models were internally validated using bootstrap resampling and externally validated on 4741 patients from the ACCORD-BP (The Action to Control Cardiovascular Risk in Diabetes blood pressure) trial. Among 9361 SPRINT patients, 755 patients (8.1%) had a MACE or death event and 338 patients (3.6%) had a treatment-related SAE during a median follow-up of 3.3 years. The MACE/death and the SAE model had C statistics of 0.72 and 0.70, respectively, in the derivation cohort and 0.69 and 0.65 in ACCORD. The MACE/death model had 10 variables including treatment interactions with age, baseline systolic BP, and diastolic BP, and the SAE model had 8 variables including treatment interaction with number of BP medications. Intensive BP treatment was associated with a mean 2.2±2.6% lower risk of MACE/death compared with standard treatment (range, 20.7% lower risk to 19.6% greater risk among individual patients) and a mean 2.2±1.2% higher risk for SAEs (range, 0.5%–15.8% more harm in individual patients).

Conclusions—To translate the findings from SPRINT to clinical practice, we developed prediction models to tailor the intensity of BP control based on the projected risk and benefit for each unique patient. This approach should be prospectively tested to better engage patients in shared medical decision making and to improve outcomes.

Clinical Trial Registration—URL: https://clinicaltrials.gov. Unique identifier: NCT01206062.

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Key Words: acute kidney injury ■ adult ■ blood pressure ■ decision making ■ hypertension
WHAT IS KNOWN

- The SPRINT trial suggests that, on average, hypertensive patient at high cardiovascular risk would have less cardiovascular morbidity and mortality but higher treatment-related adverse events with an intensive blood pressure treatment strategy as compared with a standard blood pressure treatment strategy.
- Applying these population-level results to individual patients is challenging, as each patient may have different benefits and risks than the average patient in SPRINT.

WHAT THE STUDY ADDS

- Using patient-level data from SPRINT, we developed risk prediction models that estimate an individual patient’s risk of major adverse cardiovascular events or death and treatment-related SAEs with intensive or standard BP control.
- Application of these models could potentially be used to support clinicians and patients in selecting a treatment strategy based on the patient’s specific risk factors and treatment preferences, thereby targeting treatment to those most likely to benefit and minimizing potential risk.

Outcomes

For the present analysis, we constructed 2 models, one modeling the risk of MACE or death and the other modeling the risk of treatment-related SAEs for intensive compared with standard BP treatment. Our outcome for the MACE/death model was a composite outcome of all-cause death or MACE, which included myocardial infarction (MI), acute coronary syndrome, stroke, or acute decompensated heart failure. Treatment-related SAEs were defined as events that were fatal or life threatening, resulted in clinically significant or persistent disability, required or prolonged a hospitalization, or were judged by the investigator to represent a clinically significant hazard or harm to the participant. We chose to focus on treatment-related adverse events because these were determined by the study leadership to represent the negative consequences of pursing a more aggressive treatment strategy and were deemed to be most relevant to the decision facing patients who are considering alternative intensities of BP control. All SAEs were reviewed by the trial safety officer to assess whether or not it was related to treatment, which was further reviewed monthly by the safety committee. An independent adjudication committee, blinded to the treatment assignment, adjudicated each component of these end points.2

Statistical Analyses

Baseline demographic, comorbidity, laboratory, and other clinical data were compared between patients with versus without MACE/death and those with versus without treatment-related SAE. Continuous variables were compared using Student’s t test, and categorical variables were compared using \( \chi^2 \) tests.

Model Construction

We developed separate models using logistic regression to estimate patients’ probability of MACE/death and treatment-related SAEs. We excluded patients with any missing data (n=486 [5.25%] for the MACE/death model and n=538 [5.6%] for the SAE model) for this model is 100%. We then ranked all variables by \( F \) value within this model and removed variables sequentially until removing another variable would reduce the \( R^2 \) below 95%. With this approach, the reduced model accounts for >95% of the variability in predicted values from the full model (Figures I and II in the Data Supplement). Ultimately, we retained 10 variables in the reduced MACE/death model and 8 variables in the SAE model, which accounted for >95% of the predictive capacity of the full models, respectively. All continuous effects were assessed for linearity using LOESS (LocRegrES:ion) plots, and no significant nonlinearity was found in the final model. Model discrimination was assessed with C statistics.

Internal Model Validation

Both the MACE/death and SAE models were internally validated using bootstrap resampling for 200 replications.2 For each step of resampling, the model was refit as described above, and performance (calibration slope and C statistic) was assessed on the bootstrapped data and validated on the original data set. The difference in performance between the 2 data sets was calculated and averaged over the 200 replications. The average difference estimates because of overfitting were then subtracted from the final reported performance of the full and reduced models.
External Validation

Both the risk models were externally validated within the BP arm of the ACCORD (The Action to Control Cardiovascular Risk in Diabetes) trial, conducted from January 2003 through June 2009. The trial enrolled 4741 patients with diabetes mellitus at high cardiovascular risk, randomized to receive intensive (<120 mm Hg) versus standard BP (≤140 mm Hg) treatment, followed up during a mean duration of 4.7 years. Important differences in the derivation and validation cohorts included the following: all patients in ACCORD had diabetes mellitus, as compared with none in SPRINT; ACCORD included patients with a history of stroke and congestive heart failure, all of whom were excluded from the SPRINT trial; patients with chronic kidney disease and estimated glomerular filtration rate between 20 and 60 mL·min⁻¹·m² were included in SPRINT; whereas patients with serum creatinine >1.5 mg/dL were excluded from the ACCORD trial. There were also important differences in the definition of outcomes between the 2 trials. The primary outcome for validation of MACE/death model included a combination of the primary and secondary end points to ensure comparability with the end points used in the SPRINT risk prediction model: nonfatal MI, nonfatal stroke, congestive heart failure hospitalization, and all-cause death. Importantly, ACCORD did not include non-MI acute coronary syndrome and emergency room visits related to congestive heart failure in their primary end points, whereas SPRINT did. Similarly, the outcome for SAE model was antihypertensive treatment-related SAEs. Using data from the BP arm of the ACCORD trial, we validated our MACE/death and SAE models by calculating C statistics and plotting calibration curves after applying the risk prediction equations derived from the SPRINT trial. Because of differences in the event rates between ACCORD and SPRINT populations, we recalibrated the SPRINT prediction formulas by adjusting the intercepts to match the overall ACCORD and SPRINT populations, we recalibrated the SPRINT prediction formulas by adjusting the intercepts to match the overall event rates in ACCORD. We then plotted the observed event rates in ACCORD within each decile of predicted risk using the recalibrated models. Recalibrating the intercept does not affect the risk associated with each factor or the model discrimination.

Access to the patient-level data for the ACCORD trial was obtained through National Heart, Lung, and Blood Institute BioLINCC data repository (https://biolincc.nhlbi.nih.gov/studies/accord/) after approval from the Institutional Review Board at Saint Luke’s Hospital.

Describing Heterogeneity of Treatment Effect

To understand the degree of variability in SPRINT patients’ probabilities of MACE/death and SAE from the 2 alternative BP control strategies, we calculated each participant’s predicted probability of both outcomes (MACE/death and treatment-related SAE) twice, first assuming treatment with intensive BP control and second assuming treatment with standard BP control. We identified the range of predicted absolute risks of both outcomes between the 2 treatment strategies by calculating the difference in absolute risks of MACE or death and treatment-related SAE, respectively, for each SPRINT patient if treated with intensive and standard BP control. The distribution of absolute predicted risk of benefit (MACE/death) and harm (SAE) between intensive and standard BP control across the SPRINT population was presented graphically with histograms. All analyses were conducted using SAS version 9.4 and R version 3.3.1.

Results

Study Cohort

Among 9361 patients enrolled in SPRINT, 755 patients (8.1%) had MACE or death (intensive BP control: 322/4678 [7.1%]; standard BP control 423/4683 [9.0%]), and 338 patients (3.6%) had a treatment-related SAE (intensive BP control: 220/4678 [4.7%]; standard BP control 118/4683 [2.5%]) during a median follow-up of 3.26 years. Patients who had MACE/death were more likely to be older, men, white, and current smokers; to have higher SBP but lower diastolic BP (DBP) at baseline; to have clinical or subclinical cardiovascular disease; to be on higher number of antihypertensive agents, higher 10-year Framingham cardiovascular risk, and poor renal function; and to be assigned to standard treatment arm (Table). Patients with a treatment-related SAE were more likely to be older; to have lower DBP, poor renal function, subclinical, and clinical cardiovascular disease; to be on higher number of antihypertensive agents and higher 10-year Framingham cardiovascular risk; and to be randomized to intensive BP treatment (Table).

Risk Prediction Models

The prediction models for MACE/death and treatment-related SAE are shown in Figures 1 and 2 and Tables II through V in the Data Supplement, respectively. The final model for MACE/death included 13 covariates and interactions of treatment with age, baseline SBP, and baseline diastolic BP. There was noted to be a lower risk of MACE or death from intensive BP treatment in patients with increasing age and higher baseline DBP. However, intensive BP treatment was noted to have a higher risk of MACE or death compared with standard BP treatment in patients with higher baseline SBP. The parsimonious prediction model for treatment-related SAE included 9 covariates and interaction of treatment with number of antihypertensive agents. Older age, current smoking, higher creatinine, higher urine albumin/creatinine ratio, and increasing number of antihypertensive medications at baseline were in both the MACE/death and SAE models and were associated with both higher MACE/death rates and greater SAEs with both treatment strategies. The C statistics were similar after internal bootstrap validation (C statistic=0.72 for MACE/death model and 0.70 for the SAE model). Both models showed good calibration when observed versus predicted risks for the outcomes were plotted (Figures III and IV in the Data Supplement). The MACE/death model had an intercept of −0.05 and slope of 0.98. The SAE model had an intercept of −0.14 and slope of 0.95. The SAE model overpredicted risks above 12%; however, there were few patients (n=171, 1.8%) in that category.

External Validation

The BP arm of ACCORD trial included 4741 diabetic patients at high cardiovascular risk (mean age, 62.2 years; 52.3% men, 33.7% with cardiovascular disease at baseline) followed for mean duration of 4.7 years. Among patients randomized to intensive BP treatment, 333 out of 2368 patients (14.1%, 3% per year) had MACE/death and 90 out of 2368 patients (3.8%) had a SAE. Among patients randomized to standard BP treatment in ACCORD, 367 out of 2373 patients (15.5%, 3.3% per year) had MACE/death and 41 out of 2373 patients (1.7%) had a SAE. In this cohort, the MACE/death and SAE model showed modestly reduced discrimination with C statistics of 0.69 and 0.65, respectively. After recalibration to the baseline event rates, both models showed good calibration (Figures V and VI in the Data Supplement). The MACE/death model had an intercept of 0.03 and a slope of 0.82 (R²=96.7%), with slightly higher predicted than observed rates in only the highest decile of risk. The SAE model had an intercept of 0.002 and slope of 0.93 (R²=88%).

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Predicted Benefit, Harm, and Heterogeneity of Treatment Effect

The mean predicted absolute reduction in risk of MACE/death with intensive BP treatment was of 2.2±2.6% (median, 1.6%; interquartile range, 0.7%–3.1%) compared with standard treatment but ranged from 20.7% lower risk to 19.6% greater risk in individual patients (Figure 3; Figure VII in the Data Supplement). The mean predicted absolute rate for treatment-related SAEs with intensive treatment was 2.2%±1.2% (median 1.9%; interquartile range, 1.4%–2.7%), but ranged from 0.5% to 15.8% higher compared with standard treatment (Figure 3; Figure VII in the Data Supplement). Figure VII in the Data Supplement graphically represents each SPRINT patient’s predicted absolute risk of MACE or death on the y axis against each patient’s predicted absolute harm with intensive compared with standard treatment on the x axis. Overall, 43% of all SPRINT patients would benefit from receiving intensive BP treatment over standard treatment if they valued avoiding MACE/death as equal to a treatment-related SAE, but this proportion increases if avoiding MACE/death was valued by a given patient as more important than avoiding a treatment-related SAE (Figure VII in the Data Supplement).

Discussion

Translating landmark clinical trials to clinical practice has been a pressing challenge for the medical profession. Although guidelines and performance measures have been the primary strategies, these have failed to insure that the Institute of Medicine’s goals for effective, safe, patient-centered care have been achieved. An important and underused strategy to accelerate the translation of clinical trials to practice is to build models of the heterogeneity of treatment benefit to personalize evidence-based treatment. The decision to treat BP aggressively is complex, with trade-offs in reduction in cardiovascular morbidity and mortality but more SAEs. Given these trade-offs, the SPRINT trial represents an ideal place in which to model these potential benefits and harms of intensive versus standard BP control treatment strategies. In this study, we modeled the heterogeneity in treatment effect for both benefit and harm in SPRINT and found marked variability in the benefits of intensive BP control (range of 20% worse outcomes to 21% better outcomes) and
harm (range from 0.5% to 16%), based on patient characteristics. Application of these models could potentially be used to translate the findings of the SPRINT trial to support clinicians and patients selecting a treatment strategy based on the patient’s specific risk factors, thereby targeting treatment to those most likely to benefit and minimizing potential risk.

A recent study using National Health and Nutrition Examination Surveys data estimated that a total of 16.8 million US patients with hypertension would potentially be eligible for intensive BP treatment according to the major eligibility criteria of SPRINT.1 Given the additional clinical burden of intensive BP treatment (eg, more clinic visits, more medications) and the potential for SAEs,2 understanding who is estimated to benefit the most from intensive BP treatment could be exceptionally helpful to both clinicians and patients. In particular, these models may be of most benefit to patients with SBP in the gray zone between 130 and 139 mm Hg, who are currently being treated with lifestyle changes according to the guidelines14 and account for 34.8% of all patients with hypertension in the United States.1 Use of models, such as these, to personalize treatment to patients based on their unique characteristics has the ability to target treatment to those most likely

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**Figure 1.** Risk prediction model for major adverse cardiovascular events (MACE) or death in patients with hypertension at high cardiovascular risk, with intensive compared with standard blood pressure (BP) control strategy. Odds Ratios (ORs) are presented separately for treatment with intensive and standard BP control for variables with significant interaction with BP treatment strategy. MACE includes composite of myocardial infarction, acute coronary syndrome, stroke, or acute decompensated heart failure. Clinical cardiovascular disease includes one or more of myocardial infarction, acute coronary syndrome, >50% coronary/carotid/ peripheral stenosis or revascularization or abdominal aortic aneurysm ≥5 cm.

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**Figure 2.** Risk prediction model for treatment-related serious adverse event (SAE) in patients with hypertension at high cardiovascular risk, with intensive compared with standard blood pressure control strategy. Treatment-related SAEs were side effects believed to be secondary to treatment, assessed by the trial safety officer and reviewed monthly by the safety committee. BP indicates blood pressure.
to benefit, to minimize treatment-related SAEs, and ultimately to optimize patient outcomes. Moreover, directly estimating each patient’s benefits and risks may better engage patients in their treatment decision, which could potentially improve treatment adherence.\(^{15,16}\)

Importantly, both the models performed well on external validation in the ACCORD trial participants, who differed substantially from those in the SPRINT trial by all having diabetes mellitus and 6.5% and 4.3% having had a history of stroke and congestive heart failure, respectively. The ACCORD patients also had different rates of adverse events, and there were slight differences in how these outcomes were classified (stricter definitions of end points in ACCORD that did not include non-MI acute coronary syndrome or ER visits because of congestive heart failure). Nevertheless, the model performed well in this distinct cohort of patients, although the MACE/death model slightly overpredicted risk in the highest risk decile. Finding comparable performance in a cohort of patients with vastly different baseline characteristics strongly supports the external generalizability of the SPRINT models that we created.

We noted many interesting observations among the studied population that highlight the potential advantages of precision medicine over contemporary strategies of simple univariate classification. For example, older patients have traditionally been considered to not be candidates for more intensive BP control. For example, the most recent BP management guideline has recommended higher BP goals (≤150/90 mmHg) to limit the risk of harm in older patients (≤140/90 mmHg) to limit the risk of harm in older patients.\(^{14}\) We found a significant treatment interaction with age in our model for MACE/death, suggesting that older patients were more likely to benefit from intensive BP treatment, possibly because of them being at increased cardiovascular risk. In contrast, although we found that while older patients were more likely to have SAEs, these were not greater in those with more intensive BP control, as there was no significant treatment interaction of age with SAE. Although a higher BP goal may be appropriate for some patients at advanced age, our results suggest that many of these patients may benefit from intensive treatment.

The interaction of BP treatment with patient’s baseline SBP, suggesting higher risk of MACE or death with intensive treatment in patients with higher baseline SBP may result from a larger morbidity/mortality reduction with standard BP treatment (eg, in a patient with a baseline SBP of 180 mmHg, a reduction of 40 mmHg [standard treatment] would result in a large risk reduction and may dilute the comparison of a reduction of 60 mmHg [intensive treatment]) or might be because of difficulty in achieving intensive goal BP in these patients (ie, difficult to get to 60 mmHg reduction). The treatment interaction of BP treatment with baseline DBP, suggesting higher risk of MACE events or death with intensive BP treatment in patients with lower baseline diastolic BP, may be explained by a previously demonstrated J-curve–shaped association between diastolic BP and cardiac events and all-cause mortality, especially in patients at high risk or with known coronary artery disease.\(^{17-19}\) Intensive BP treatment in patients with lower baseline DBP could possibly result in low DBPs that subsequently increase patients’ risk of ischemia and death.\(^{20}\) Our risk prediction models can enable providers to integrate age and BP, along with multiple other risk factors, to estimate patients’ risks and benefits directly without using coarse, single-variable associations to define optimal treatment.

Our findings should be interpreted in the context of several potential limitations. Because we were limited to analyzing the publicly released data, particular data elements that might be prognostically important, such as type of clinical cardiovascular disease, were not available for consideration in our models. Factors that influence medication adherence, such as socioeconomic factors, social support, and depression could also potentially alter the effectiveness of intensive BP treatment and the end point of MACE/death. Similarly, other factors, such as frailty and specific drug classes, could also affect treatment-related SAEs. However, none of these characteristics were available and could not be used for model development. It must also be acknowledged that patients enrolled in clinical trials are generally healthier, more compliant with
treatments, and better monitored for safety than patients in the real world.21 Furthermore, the BPs achieved in SPRINT were under ideal trial conditions with close follow-up.22 As such, whether or not real-life practice could result in similar benefits or harms as those predicted by SPRINT will need to be tested in future studies.22 We used combined outcomes for both assessment of benefit and harm. Patients may value preventing death differently than preventing heart failure, MI, or stroke; however, we felt that all these outcomes are clinically important outcomes for prevention. Additionally, we chose to present the patients and clinicians with individualized risk estimates for MACE/death and SAE with different BP treatment strategies and have them make a decision regarding the choice of therapy based on their own preferences and goals, rather than making fixed assumptions regarding how they should weigh the risks versus benefits with each strategy and providing a single treatment recommendation. Also, although we did find evidence of some treatment interactions suggesting heterogeneity in treatment effect, there might be other interactions that we did not have the power to detect.23

In conclusion, using data from a large clinical trial of patients with hypertension and high cardiovascular risk, we developed risk models that estimate a specific patient’s personal risk of benefit and harm with intensive or standard BP control. These models represent an important step forward in the field of precision medicine by enabling the results of a landmark clinical trial to be used in routine patient care to tailor the treatment approach based on the projected risk and benefit for each unique patient. Involving patients prospectively in clinical decision making using individualized risk estimates could also potentially help improve treatment adherence and outcomes. Further studies are needed to understand the clinical impact of using these models in care and defining how these models perform in low-risk, younger patients with hypertension.

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Disclosures

Dr Chan serves as a consultant for Optum Rx (significant). Dr Spertus serves as a consultant to United Healthcare, Bayer, and Novartis (modest). He has research grants from Abbott Vascular and Novartis and is the PI of an analytic center for the American College of Cardiology (significant). He has an equity interest in Health Outcomes Sciences (significant). The other authors report no conflicts.

References

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Data Supplement (unedited) at:
http://circoutcomes.ahajournals.org/content/suppl/2017/04/03/CIRCOU10.003624.DC1

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SUPPLEMENTAL MATERIAL
For
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Yashashwi Pokharel, MD, MSCR; Philip G Jones, MS; John A Spertus, MD MPH
Supplement Table 1: Candidate variables introduced for development of both risk models

<table>
<thead>
<tr>
<th>MACE/Death model</th>
<th>Treatment-related Serious Adverse Event model</th>
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<tbody>
<tr>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Sex</td>
<td>Sex</td>
</tr>
<tr>
<td>Race</td>
<td>Race</td>
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<tr>
<td>Intensive treatment strategy</td>
<td>Intensive treatment strategy</td>
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<td>Body mass index</td>
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<tr>
<td>Systolic blood pressure</td>
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<tr>
<td>Diastolic blood pressure</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>History of subclinical CVD</td>
<td>History of subclinical CVD</td>
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<tr>
<td>History of clinical CVD</td>
<td>History of clinical CVD</td>
</tr>
<tr>
<td>Number of anti-hypertensive agents</td>
<td>Number of anti-hypertensive agents</td>
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<tr>
<td>Current Smoker</td>
<td>Current Smoker</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>Serum Creatinine</td>
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<tr>
<td>Urine Albumin/Creatinine ratio</td>
<td>Urine Albumin/Creatinine ratio</td>
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<tr>
<td>Total Cholesterol/HDL Cholesterol ratio</td>
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<tr>
<td>Fasting Serum Triglycerides</td>
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<tr>
<td>Fasting Plasma Glucose</td>
<td></td>
</tr>
<tr>
<td>Aspirin use</td>
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</tr>
<tr>
<td>Statin use</td>
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</table>

We also tested interactions for all the other variables listed above with randomized intensive treatment arm for both the models.

MACE= composite of myocardial infarction (MI), acute coronary syndrome not resulting in MI, stroke or acute decompensated heart failure. CVD= cardiovascular disease, clinical CVD includes one or more of myocardial infarction, acute coronary syndrome, > 50% coronary/carotid/peripheral artery stenosis or revascularization; or abdominal aortic aneurysm ≥5 mm; subclinical CVD includes one or more of coronary artery calcium score ≥400, ankle-brachial index ≤0.90, or left ventricular hypertrophy.
Supplement Table 2: Predicting risk of Major Adverse Cardiovascular Events or Death (Reduced model)
The table below contains the SPRINT trial-estimated logistic regression coefficients for the significant risk factors that entered the ischemia model.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Regression Coefficient</th>
<th>Standard Error</th>
<th>p-value*</th>
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<td>0.7686</td>
<td>&lt;.0001</td>
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<td>Number of anti-hypertensive agents</td>
<td>0.08255</td>
<td>0.04023</td>
<td>0.0402</td>
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<tr>
<td>INTENSIVE * Age (per 10 years)</td>
<td>-0.2098</td>
<td>0.1016</td>
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<tr>
<td>INTENSIVE* DBP ( +10mmHg)</td>
<td>-0.2079</td>
<td>0.08748</td>
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<td>Diastolic Blood Pressure (+10 mmHg)</td>
<td>0.09082</td>
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<td>INTENSIVE*SBP (+10mmHg)</td>
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<tr>
<td>Systolic Blood Pressure (+10 mmHg)</td>
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<td>Total cholesterol/HDL cholesterol ratio</td>
<td>0.1323</td>
<td>0.03323</td>
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<td>Serum Creatinine</td>
<td>0.4399</td>
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<td>&lt;.0001</td>
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<td>Log urine Albumin/Creatinine Ratio</td>
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<tr>
<td>Age (+10 years)</td>
<td>0.5862</td>
<td>0.07026</td>
<td>&lt;.0001</td>
</tr>
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</table>

*derived from reduced model

The predicted risk for a given individual is calculated as follows ( substitute 1 or 0 for presence or absence of categorical variables: intensive BP treatment, current smoker, history of clinical CVD includes one or more of myocardial infarction, acute coronary syndrome, > 50% coronary/carotid/peripheral artery stenosis or revascularization; or abdominal aortic aneurysm ≥5 mm) =1/(1+EXP(-(-8.485+ 0.08255*(no of anti-hypertensive agents) -0.2098*(Age/10)*(Intensive treatment) -0.2079*(DBP/10)*(Intensive treatment))
+0.09082*(DBP/10) +0.1665*(SBP/10)*(Intensive treatment)-0.05565*(SBP/10) +0.1323*(TC/HDL-C ratio) +0.4399*(serum creatinine) +0.4199*(Intensive treatment) +0.7471*(current smoker) +0.8066*(history of clinical CVD) +0.2671*(log_{10}(urine albumin/creatinine ratio)+0.5862*(age/10))
Supplement Table 3: Predicting risk of Treatment-related Serious Adverse Events (Reduced model)
The table below contains the SPRINT trial-estimated logistic regression coefficients for the significant risk factors that entered the harm model.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Regression Coefficient</th>
<th>Standard Error</th>
<th>p-value*</th>
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<tr>
<td>Intercept</td>
<td>-8.8694</td>
<td>0.7168</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Systolic blood pressure (+10mmHg)</td>
<td>0.04573</td>
<td>0.03689</td>
<td>0.2151</td>
</tr>
<tr>
<td>INTENSIVE * no of antihypertensive agents</td>
<td>-0.1677</td>
<td>0.1152</td>
<td>0.1454</td>
</tr>
<tr>
<td>Male gender (Yes=1, No=0)</td>
<td>-0.1510</td>
<td>0.1236</td>
<td>0.2218</td>
</tr>
<tr>
<td>Log urine Albumin/Creatinine Ratio</td>
<td>0.1019</td>
<td>0.04621</td>
<td>0.0275</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>0.6224</td>
<td>0.1425</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Current Smoker (Yes=1, No=0)</td>
<td>0.6468</td>
<td>0.1665</td>
<td>0.0001</td>
</tr>
<tr>
<td>Number of anti-hypertensive agents</td>
<td>0.3584</td>
<td>0.09382</td>
<td>0.0001</td>
</tr>
<tr>
<td>Intensive BP treatment (Yes=1, No=0)</td>
<td>1.0290</td>
<td>0.2824</td>
<td>0.0003</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>0.4080</td>
<td>0.06446</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*derived from reduced model

The predicted risk for a given individual is calculated as follows: 
( substitute 1 or 0 for presence or absence of categorical variables: intensive BP treatment, current smoker, male gender) 
$$= 1 / (1 + \exp(-8.8694 + 0.04573 \times \text{Systolic blood pressure/10} + 0.1019 \times \log_{10}(\text{urine albumin/creatinine ratio}) + 0.6224 \times \text{serum creatinine} + 0.6468 \times \text{current smoker} + 0.3584 \times \text{number of antihypertensive agents} + 1.0290 \times \text{intensive BP treatment} + 0.4080 \times \text{Age/10} - 0.1677 \times \text{Intensive BP treatment} \times \text{no of antihypertensive agents} - 0.1510 \times \text{male gender}))$$
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio (Intensive BP treatment)</th>
<th>95% Confidence Intervals (Intensive BP treatment)</th>
<th>Odds Ratio (Standard BP treatment)</th>
<th>95% Confidence Intervals (Standard BP treatment)</th>
<th>p-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.4358</td>
<td>(1.2123, 1.7005)</td>
<td>1.8439</td>
<td>(1.5879, 2.1412)</td>
<td>0.03</td>
</tr>
<tr>
<td>Systolic BP (+10 mmHg)</td>
<td>1.115</td>
<td>(1.02, 1.2188)</td>
<td>0.9484</td>
<td>(0.872, 1.0315)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic BP (+10 mmHg)</td>
<td>0.898</td>
<td>(0.7864, 1.0255)</td>
<td>1.0896</td>
<td>(0.9668, 1.228)</td>
<td>0.03</td>
</tr>
<tr>
<td>Number of Anti-Hypertensive Medications</td>
<td>1.0434</td>
<td>(0.9228, 1.1798)</td>
<td>1.1235</td>
<td>(1.0076, 1.2528)</td>
<td>0.38</td>
</tr>
<tr>
<td>Total/HDL cholesterol Ratio (per 1 unit increase)</td>
<td>1.1132</td>
<td>(0.9714, 1.2757)</td>
<td>1.1179</td>
<td>(0.9787, 1.2769)</td>
<td>0.97</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>2.1936</td>
<td>(1.5579, 3.0889)</td>
<td>2.1853</td>
<td>(1.5744, 3.0333)</td>
<td>0.99</td>
</tr>
<tr>
<td>History of Clinical CVD</td>
<td>2.4913</td>
<td>(1.8692, 3.3203)</td>
<td>1.9584</td>
<td>(1.5078, 2.5437)</td>
<td>0.22</td>
</tr>
<tr>
<td>Serum Creatinine (+1 mg/dL)</td>
<td>1.7874</td>
<td>(1.3055, 2.4474)</td>
<td>1.3159</td>
<td>(0.9734, 1.7791)</td>
<td>0.17</td>
</tr>
<tr>
<td>Log Urine Albumin/Creatinine Ratio (per 1 log increase)</td>
<td>1.3059</td>
<td>(1.1917, 1.431)</td>
<td>1.303</td>
<td>(1.1972, 1.4181)</td>
<td>0.97</td>
</tr>
<tr>
<td>Male vs Female</td>
<td>0.9072</td>
<td>(0.6878, 1.1964)</td>
<td>1.3235</td>
<td>(1.0297, 1.7013)</td>
<td>0.05</td>
</tr>
<tr>
<td>Black vs Other</td>
<td>0.936</td>
<td>(0.6931, 1.2639)</td>
<td>0.9241</td>
<td>(0.7088, 1.2046)</td>
<td>0.95</td>
</tr>
<tr>
<td>BMI (per 10 kg/m²)</td>
<td>1.1282</td>
<td>(0.9014, 1.412)</td>
<td>1.046</td>
<td>(0.8452, 1.2944)</td>
<td>0.63</td>
</tr>
<tr>
<td>History of Subclinical CVD</td>
<td>1.2127</td>
<td>(0.7758, 1.8958)</td>
<td>1.1568</td>
<td>(0.75, 1.7841)</td>
<td>0.88</td>
</tr>
<tr>
<td>Triglycerides (per 10 mg/dL)</td>
<td>0.9974</td>
<td>(0.979, 1.0161)</td>
<td>1.0043</td>
<td>(0.9876, 1.0214)</td>
<td>0.59</td>
</tr>
<tr>
<td>Fasting plasma Glucose (per 10 mg/dL)</td>
<td>0.9843</td>
<td>(0.9016, 1.0746)</td>
<td>1.0518</td>
<td>(0.9698, 1.1406)</td>
<td>0.28</td>
</tr>
<tr>
<td>Statin</td>
<td>0.9362</td>
<td>(0.7127, 1.2297)</td>
<td>0.9157</td>
<td>(0.7214, 1.1624)</td>
<td>0.90</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1.17</td>
<td>(0.8962, 1.5274)</td>
<td>0.9637</td>
<td>(0.7656, 1.2131)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

BP= blood pressure; BMI= body-mass index; CVD= cardiovascular disease; clinical CVD includes one or more of MI, ACS, > 50% coronary/ carotid/ peripheral stenosis or revascularization or AAA ≥5 cm; subclinical CVD includes one or more of coronary artery calcium score ≥400, ankle-brachial index ≤0.90, or left ventricular hypertrophy.
Supplement Table 5: Predicting risk for Treatment-related Serious Adverse Events (Full model)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Odds Ratio (Intensive BP treatment)</th>
<th>95% Confidence Intervals (Intensive BP treatment)</th>
<th>Odds Ratio (Standard BP treatment)</th>
<th>95% Confidence Intervals (Standard BP treatment)</th>
<th>p-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.5803</td>
<td>(1.3006, 1.9201)</td>
<td>1.3922</td>
<td>(1.0709, 1.8099)</td>
<td>0.45</td>
</tr>
<tr>
<td>Number of Anti-Hypertensive Medications</td>
<td>1.1932</td>
<td>(1.0342, 1.3767)</td>
<td>1.3997</td>
<td>(1.1527, 1.6995)</td>
<td>0.19</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>1.7399</td>
<td>(1.1376, 2.6613)</td>
<td>2.1529</td>
<td>(1.2384, 3.7427)</td>
<td>0.55</td>
</tr>
<tr>
<td>Serum Creatinine (+1 mg/dL)</td>
<td>1.9003</td>
<td>(1.3267, 2.7219)</td>
<td>1.7279</td>
<td>(1.0746, 2.7784)</td>
<td>0.75</td>
</tr>
<tr>
<td>Log Urine Albumin/Creatinine Ratio (per 1 log increase)</td>
<td>1.0889</td>
<td>(0.9721, 1.2197)</td>
<td>1.1327</td>
<td>(0.9732, 1.3184)</td>
<td>0.68</td>
</tr>
<tr>
<td>Male vs Female</td>
<td>0.8981</td>
<td>(0.6538, 1.2337)</td>
<td>0.7596</td>
<td>(0.5034, 1.1463)</td>
<td>0.53</td>
</tr>
<tr>
<td>Black vs Other</td>
<td>0.9746</td>
<td>(0.6939, 1.3689)</td>
<td>1.1411</td>
<td>(0.7381, 1.7642)</td>
<td>0.58</td>
</tr>
<tr>
<td>BMI (per 10 kg/m²)</td>
<td>1.0611</td>
<td>(0.8175, 1.3772)</td>
<td>1.0331</td>
<td>(0.7233, 1.4757)</td>
<td>0.91</td>
</tr>
<tr>
<td>Systolic BP (+10 mmHg)</td>
<td>1.0298</td>
<td>(0.9245, 1.147)</td>
<td>1.0788</td>
<td>(0.9356, 1.244)</td>
<td>0.61</td>
</tr>
<tr>
<td>Diastolic BP (+10 mmHg)</td>
<td>1.0282</td>
<td>(0.8772, 1.2052)</td>
<td>0.9507</td>
<td>(0.7731, 1.1691)</td>
<td>0.56</td>
</tr>
<tr>
<td>History of Clinical CVD</td>
<td>1.1959</td>
<td>(0.8434, 1.6958)</td>
<td>1.1447</td>
<td>(0.7142, 1.8347)</td>
<td>0.88</td>
</tr>
<tr>
<td>History of Subclinical CVD</td>
<td>1.4041</td>
<td>(0.8343, 2.3632)</td>
<td>1.2163</td>
<td>(0.574, 2.5774)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

BP= blood pressure; BMI= body-mass index; CVD= cardiovascular disease; clinical CVD includes one or more of MI, ACS, > 50% coronary/ carotid/ peripheral stenosis or revascularization or AAA ≥5 cm; subclinical CVD includes one or more of coronary artery calcium score ≥400, ankle-brachial index ≤0.90, or left ventricular hypertrophy.
Supplement Figure 1: Frank-Harrell approach of derivation of parsimonious predictive MACE/Death model from full model.

All variables ranked by F-value within the model, and variables are sequentially removed until removing another variable would reduce the R-square below 95%. With this approach, the reduced model accounts for >95% of the variability in predicted values from the full model. (INTENSIVE= Intensive BP treatment randomization; variable * INTENSIVE shows the interaction between intensive BP treatment and that variable; BP= blood pressure; CVD= cardiovascular disease; clinical CVD includes one or more of MI, ACS, > 50% coronary/ carotid/ peripheral stenosis or revascularization or AAA ≥5 cm; subclinical CVD includes one or more of coronary artery calcium score ≥400, ankle-brachial index ≤0.90, or left ventricular hypertrophy; TC: total cholesterol, HDL-C:HDL cholesterol)
All variables ranked by F-value within the model, and variables are sequentially removed until removing another variable would reduce the R-square below 95%. With this approach, the reduced model accounts for >95% of the variability in predicted values from the full model. (INTENSIVE= Intensive BP treatment randomization; variable * INTENSIVE shows the interaction between intensive BP treatment and that variable; BP= blood pressure; CVD= cardiovascular disease; clinical CVD includes one or more of MI, ACS, > 50% coronary/ carotid/ peripheral stenosis or revascularization or AAA ≥5 cm; subclinical CVD includes one or more of coronary artery calcium score ≥400, ankle-brachial index ≤0.90, or left ventricular hypertrophy)
Supplement Figure 3: Calibration curve for the reduced Major Adverse Cardiovascular Events or Death model derived after bootstrap validation

Model intercept = -0.0503, Slope = 0.9752
Supplement Figure 4: Calibration curve for the reduced Treatment-related Serious Adverse Event model derived after bootstrap validation

Model intercept = -0.1387, Slope = 0.9521. The SAE model over-predicted risks above 12%, however there were very few patients (n=171, 1.8%) in that category.
Supplement Figure 5: Calibration curve showing observed vs. predicted risks of MACE/death in the ACCORD trial population using risk equations developed from SPRINT trial

Model intercept = 0.03; Slope = 0.82; $R^2 = 96.7\%$. The MACE/death model overpredicted risks in the highest decile.
Supplement Figure 6: Calibration curve showing observed vs. predicted risks of treatment-related SAE in the ACCORD trial population using risk equations developed from SPRINT trial

Model intercept= 0.002; Slope= 0.93, $R^2 = 88\%$
Supplement Figure 7: Net predicted probability of benefit and harm for each individual patient in the Systolic blood Pressure Intervention Trial. Figure legend on next page.

Reference lines represent thresholds to identify net benefit (benefit: harm ratios) with intensive compared to standard treatment.
Dots represent each patient’s net predicted probability of major adverse cardiovascular events (MACE) or death and treatment-related SAE. Predicted risk of any treatment related serious adverse event; (intensive- standard treatment) is plotted on x-axis against net predicted risk of MACE or death (standard-intensive treatment) on y-axis. The further to the right on x-axis, the greater the harm with intensive treatment; the higher on the y-axis, the greater the benefit with intensive treatment. The lines represent the thresholds for identifying net-benefit with intensive treatment; patients to the left and above the line corresponding to ratios of 1, 0.5, 0.33 and 0.25 (43%, 72.6%, 80.7% and 83.7% of the population respectively) are likely to derive net benefit from intensive treatment if they value MACE or death at least equal to or greater than two, three and four times more important than treatment-related SAE.