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## **Individualizing treatment choices in the SPRINT trial**

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## **Abstract**

**Background:** Any treatment decision should be tailored to the individual patients' characteristics. A personalized approach aims to help better selecting the patients who are likely to benefit most from a treatment decision. In the SPRINT trial, intensive treatment reduced the rate of major cardiovascular events, but increased the rate of serious adverse events.

**Objectives:** To assess the trade-off between efficacy and safety to simultaneously quantify an individual patient's absolute benefit and absolute harm, helping clinicians making better therapeutic choices in daily practice.

**Methods:** Multivariable [Cox-Poisson regression](#) models were used to identify independent risk factors for: 1) primary composite cardiovascular outcome=efficacy, and 2) major serious adverse events (SAEs)=safety. Estimates from the models were used to quantify each individual risk.

**Results:** Sub-clinical cardiovascular disease, number anti-hypertensive agents, current smoking, age, urine albumin to creatinine ratio, and serum creatinine were associated with increased risk of both primary outcome events and SAEs. Triglycerides were associated with increased primary outcome events only, and chronic kidney disease and female sex with SAEs only. The models were well calibrated and showed good performance (c-index for safety=0.69 and c-index for efficacy=0.72). For the primary outcome, there is a steep gradient in risk by fifths of the predicted model and a similar gradient exists for the safety outcome predicted model. Mortality within 1-year of an efficacy outcome (as assessed by the Kaplan-Meier method) was nearly 3-fold higher than following a safety outcome (21.9% vs. 7.5%). If one judges the clinical importance of efficacy and safety outcomes based on their 1-year mortality, then there is a net benefit of intensive therapy for almost all patients.

**Conclusion:** Anti-hypertensive treatment intensification is associated with lower cardiovascular event rates however it increases the risk of adverse events. The present analysis helps clinicians to perform individualized treatment decisions based on readily available risk models.

**Key-words:** individualized anti-hypertensive treatment decisions; SPRINT trial; benefits; harms; intensive therapy.

## **Introduction**

Individualized treatment decisions, also referred to as “personalized approach” is warranted to better select patients who will likely benefit most from a therapeutic decision. The potential benefits must be weighed against the potential harms, in a “trade-off” analysis that takes into account both the severity associated with an efficacy event and that associated with a safety adverse event. For example, if mortality is greatly increased after a non-fatal primary efficacy event, but not after an adverse event, then treating a patient will likely be beneficial even if an adverse event occurs along the way. In other words, a balanced account of both efficacy and safety must be provided<sup>1</sup>. Consideration of the number needed to treat for benefit versus the number needed to harm may provide a guide to net clinical benefit as long as the clinical severity of the events is taken into account<sup>2</sup>.

In the SPRINT (A Randomized Trial of Intensive versus Standard Blood-Pressure Control) trial<sup>3</sup>, intensive anti-hypertensive treatment with the goal of lowering systolic blood pressure below 120 mmHg resulted in a lower rate of the primary composite cardiovascular outcome (-1.6%) and a lower rate of death (-1.2%), compared to the rates observed with standard blood-pressure control (goal <140 mmHg). The benefits of intensive blood pressure lowering must be weighed against the increase in the serious adverse event rate. However, significantly higher rates of serious adverse events (SAEs) were observed in the intensive-treatment group, including reported serious adverse events or adverse events requiring emergency visit. For example, symptomatic hypotension (+1.4%), syncope (+1.1%), electrolyte abnormalities (+1%), and acute kidney injury or failure (+1.8%). Despite the small absolute difference in the benefits and risks, guideline committees, treating physicians, and patients may face a challenge when trying to determine which strategy to adopt. Hence, a “trade-off” analysis of potential benefits and harm may help in daily decision of whether intensify or not anti-hypertensive treatment in each individual patient.

The main aims of the present analysis are: 1) to separately assess the absolute efficacy and the absolute safety of an intensive strategy vs. a standard strategy for individual patients whose risk profiles vary markedly; 2) to compute the theoretical net benefit associated with each patient profile; and 3) estimate the distributions of these net benefits on the whole SPRINT population.

## **Methods**

### **Trial oversight**

SPRINT was sponsored by the NHLBI, with co-sponsorship by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, and the National Institute on Aging. The rationale and protocol for the trial have been previously published<sup>3</sup> and are publicly available<sup>4</sup>.

In short, participants were required to meet all the following criteria: an age of at least 50 years, a systolic blood pressure of 130 to 180 mm Hg, and an increased risk of cardiovascular events (defined by one or more of the following: clinical or subclinical cardiovascular disease other than stroke; chronic kidney disease with an estimated glomerular filtration rate [eGFR] of 20 to 60 ml/min/1.73m<sup>2</sup>; a 10-year risk of cardiovascular disease  $\geq$ 15% on the basis of the Framingham risk score; or an age  $\geq$ 75 years). Patients with diabetes mellitus or prior stroke were excluded. All participants provided written informed consent. Eligible participants were assigned to a systolic blood-pressure target of either less than 140 mm Hg (the standard-treatment group) or less than 120 mm Hg (the intensive-treatment group). Participants and study personnel were aware of the study-group assignments, but outcome adjudicators were not. The protocol encouraged, but did not mandate, the use of drug classes with the strongest evidence for reduction in cardiovascular outcomes<sup>5</sup>. Treatment adjustment was based on a mean of three blood-pressure measurements at an office visit while the patient was seated after 5 minutes of quiet rest; the measurements were made with the use of an automated measurement system (Model 907, Omron Healthcare). A structured interview was used in both groups every 3 months to obtain self-reported cardiovascular disease outcomes. Medical records and electrocardiograms were obtained for documentation of events. Whenever clinical site staff became aware of a death, a standard protocol was used to obtain information on the event. Serious adverse events were defined as events that were fatal or life-threatening, that resulted in clinically significant or persistent disability, that required or prolonged a hospitalization, or that were judged by the investigator to represent a clinically significant hazard or harm to the participant. A list of monitored conditions was also reported as adverse events if they were evaluated in an emergency department: hypotension, syncope, injurious falls, electrolyte abnormalities, and bradycardia. Occurrences of acute kidney injury or acute renal failure were also documented. The relationship of serious adverse events to the intervention was assessed by the trial safety officer and reviewed monthly by the safety committee. A total of 9361 participants were randomized in the SPRINT trial. The trial was stopped earlier than expected after analyses of the primary outcome exceeded the monitoring boundaries at two consecutive time-points. The median follow-up was 3.26 years.

### Study Outcomes

The primary outcome [of the SPRINT trial](#) was a composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes. [In the present analysis, the primary outcome is referred to as the primary efficacy outcome.](#) [Compared with a standard systolic blood pressure target <140 mm Hg, the primary outcome was reduced by using an intensive systolic blood pressure target <120 mm Hg resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause \(6.8% vs 5.2% vs 6.8%; hazard ratio \[HR\]=0.75; 95% confidence interval \[CI\]=0.64-0.89; p<0.001\).](#) [However-Secondary](#)

outcomes included the individual components of the primary composite outcome, death from any cause, and the composite of the primary outcome or death from any cause.

Compared with a systolic blood pressure target  $<140$  mm Hg, an intensive systolic blood pressure target  $<120$  mm Hg resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause (5.2% vs. 6.8%; hazard ratio [HR] = 0.75; 95% confidence interval [CI] = 0.64–0.89;  $p < 0.001$ ). However, the SPRINT trial also reported significantly higher rates of SAEs were observed in the intensive treatment group, including that several reported serious adverse events requiring emergency room visit, as occurring more frequently in the intensive blood pressure monitoring. In particular, created a short-list of closely monitored serious adverse events consisting of the following conditions: ~~ser~~ adverse events requiring emergency visit (symptomatic hypotension: (3.4% intensive vs. 2.0% standard,  $p < 0.001$ ); syncope: (3.5% vs. 2.4%,  $p = 0.003$ ); bradycardia: (2.2% vs. 1.8%,  $p = 0.13$ ); electrolyte abnormalities: (3.8% vs. 2.8%,  $p = 0.006$ ); and acute kidney injury or failure: (4.4% vs. 2.6%,  $p < 0.001$ ). In the present analysis we define the composite safety outcome as the time to occurrence of any of the above conditions.

In the present analysis, the study primary outcome was set as the efficacy outcome, and the composite of SAEs was set as the safety outcome.

### Statistical analysis

In descriptive analyses, continuous variables are expressed as mean  $\pm$  standard deviation (SD) or median (percentile<sub>25</sub>–75 interquartile range) based on their distribution assess by visual inspection. Categorical variables are expressed as frequencies and proportions (%). Population description and comparison of patients with “events” vs. “no events” was performed using independent samples t-test for normally distributed continuous variables, Mann-Whitney test for skewed variables, and chi-square test for categorical variables. ~~No multiple imputation was performed.~~

We graphically compared time to each of the primary efficacy and composite safety outcomes using Kaplan Meier curves. Since the rate of both outcomes was similar throughout the trial we additionally report annualized rates calculated from Poisson regression models. We compared the rate of mortality occurring after each outcome using the Kaplan Meier method, where the index time was defined as the date of occurrence of the event, and the time to mortality as the time between the event and death.

To identify risk factors associated with each outcome, we used ~~Using the total SPRINT trial population, multivariable Cox-Poisson regression models were used to identify independent risk factors for: 1) primary outcome = efficacy and 2) with forward stepwise variable selection, using  $p < 0.05$  as the criteria for inclusion. We considered the following patient characteristics for inclusion in the prognostic models: sex, age, race, smoking status, systolic and diastolic blood pressure, body mass index, total cholesterol, triglycerides, glucose, urine albumin to creatinine ratio, serum creatinine, statin and aspirin use, number of antihypertensive medications, prior cardiovascular~~

disease history (clinical and/or subclinical) and presence of chronic kidney disease. We split continuous characteristics into tenths and compared risk across tenths in order to assess the correct functional form to enter into the model. There was only a small amount of missing data (6.4%), therefore we did not perform multiple imputation and we therefore performed covariate selection on the subset of patients with complete information on all candidate covariates (N=8,764), and subsequently reported risk ratios using all patients with complete information on selected covariates (N=8,885). ~~No multiple imputation was performed.~~ We assessed interactions with intensive blood pressure lowering for each of the primary efficacy outcome and composite safety outcome with baseline age, sex, baseline systolic and diastolic blood pressure, but none were significant (all  $p > 0.05$ ).

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~~The subtraction of the predicted risk with intensification from the predicted risk without intensification provided the absolute risk difference attributed to the intensification. The effect of intensification was assumed to be constant regardless of patient characteristics. for efficacy and safety respectively.~~ major SAEs composite —safety. Estimates from the models were used to assess individuals' risk by categorizing participants into five risk categories both for efficacy and safety. To simplify the risk score, integer points were assigned to each prognostic factor based upon the log-hazard ratio estimates. The total risk score for each patient was calculated by summing the points across all chosen prognostic variables. ~~The subtraction of the predicted risk with intensification from the predicted risk without intensification provided the absolute risk difference attributed to the intensification, for efficacy and safety respectively.~~ Comparing for each individual the absolute predicted benefit to the absolute predicted harm allowed to determine whether benefit outweighs clearly harms, whether harms outweighs clearly benefit, or whether both are of the same magnitude. Within each risk category the number of events, person years at risk, and the overall event rate were calculated. Kaplan-Meier plots were drawn to show the cumulative incidence curves by treatment group and risk category. The hazard ratio for "intensive therapy" vs. "standard therapy" was estimated in each risk group using a Cox proportional hazard model and the treatment by risk group interaction. Individual patient baseline data available and considered for inclusion in the prognostic model included sex, age, race, smoking status, systolic and diastolic blood pressure, body mass index, total cholesterol, triglycerides, glucose, urine albumin to creatinine ratio, serum creatinine, statin and aspirin use, number of antihypertensive medications, prior cardiovascular disease history (clinical and/or subclinical) and presence of chronic kidney disease. Linear effects and interactions (including treatment by predictor interactions) were investigated using likelihood ratio tests. Continuous variables were checked for linearity and worked to meet the proportional hazards assumptions. Categorization of continuous variables was performed using a combination of established clinical cut points, expert advice, and graphical examination of rates across quintiles.

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All analysis were performed with STATA® software (version 14).

## Results

The SPRINT trial population consisted of 9361 patients with a mean age of 70 (SD=9), of whom 64.4% were male, with a mean baseline blood pressure of 139.7 (SD=15.6). Baseline characteristic were well balanced across treatment groups. The primary efficacy outcome occurred in 243 patients in the intensive-treatment arm and 319 patients in the control arm and 243 patients in the (risk ratio: 0.75, 95% CI 0.64 to 0.89), whereas the composite safety outcome occurred in 521 intensive-treatment patients and 406 control patients, XXX patients (risk ratio: 1.30, 95% CI 1.14 to 1.48) (Figure 1 & Table 1).

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Amongst the 562927 patients who had a composite safety outcome 59 (7.5%) patients died within one year, whilst amongst the 562 patients with a primary efficacy outcome event 119 (21.9%) died within a year, representing a risk of death 2.92 primary efficacy outcome, 119 (21.9%) died within, with no clear evidence of any difference in the mortality risk between the intensive and standard groups (XX.X% vs X.XX%, p=0.16) (Figure 2). The risk of death within a year of the composite safety outcome was 7.5% (59/927), again

times higher within the first year with a primary outcome rather than a composite safety outcome event (p<0.001, Figure 2). There was no clear evidence that risk of death following a primary efficacy outcome differed between the intensive and standard group (23.8% vs 19.5%, p=0.16), nor was there any evidence that risk of death following a composite safety outcome differed between treatment groups (8.2% vs. 6.9%%, p=0.28 respectively).

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Table 2 shows the covariates selected for each of the two risk models were created, one for efficacy and another for safety. Sub-clinical cardiovascular disease, number anti-hypertensive agents, current smoking, age, urine albumin to creatinine ratio, and serum creatinine were associated with increased risk of both primary outcome events and SAEs. Triglycerides were associated with increased primary outcome events only, and chronic kidney disease and female sex with SAEs only. The models were well calibrated and showed good performance discrimination (c-index for safety=0.69 and c-index for efficacy=0.72). For the both outcomes primary outcome, there is a steep gradient in risk by fifths of the predicted model risk (Figure 3). A similar gradient exists for the safety outcome predicted model.

However, because the covariates included in each risk model were similar, the predicted risk of a primary efficacy outcome and composite safety outcome were models showed highly correlation correlated (Pearson=0.80; Figure 4)79), meaning that patients at high risk of the efficacy outcome also



tended to be at high risk of the safety outcome. As a consequence, ~~For the primary outcome, there is a steep gradient in risk by fifths of the predicted model. A similar gradient exists for the safety outcome predicted model.~~ The trade-off ~~of in~~ predicted absolute efficacy benefit ~~versus-versus~~ predicted absolute safety harm tended to be similar for most patients (Figure 5). ~~for an intensive treatment strategy in all the 9361 individuals is shown in the Figure 1.~~ If the efficacy and safety outcomes were considered clinically similar, then ~~the few patients would have a net benefit from intensive treatment majority of patients (10.9%, 972/8885) would have a net loss by intensive treatment, since (the composite safety outcomes occurred more frequently) than the primary efficacy outcome.~~ However, mortality within 1 year of an efficacy outcome was nearly 3 fold higher than following a safety outcome (21.9% vs. 7.5%). If one judges the clinical importance of efficacy and safety outcomes based on their 1-year mortality, then there is a net benefit of intensive therapy for almost all patients (98.4%, 8743/8885).

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## Discussion

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## Conclusion

Anti-hypertensive treatment intensification is associated with lower cardiovascular event rates however it increases the risk of adverse events. The present analysis helps clinicians to perform individualized treatment decisions based on readily available risk models. For any hypertensive patient (without diabetes or prior stroke) knowing his predicted absolute ~~3-year annual~~ cardiovascular benefit and his predicted absolute ~~annual 3-year~~ harm for adverse events will aid clinical judgement as to whether therapy intensification is warranted.

Table 1: Baseline characteristics by treatment group

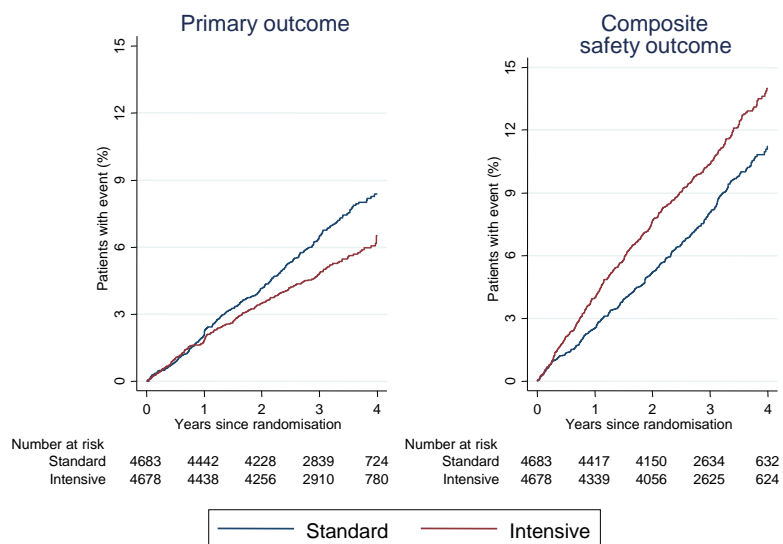
**Table 12:** Frequency of primary outcome, composite safety outcome and their components by treatment group

Outcome	Standard		Intensive		% difference in annual event rate (95% CI)	Relative risk (95% CI)	P-value
	N event	Annual event rate (%)	N event	Annual event rate (%)			
Primary outcome	243	1.7%	319	2.2%	-0.5 (-0.9 to -0.2)	0.75 (0.64 to 0.89)	0.0009
Myocardial infarction	97	0.7%	116	0.8%	-0.1 (-0.3 to 0.1)	0.83 (0.63 to 1.09)	0.1795
Acute coronary syndrome	40	0.3%	40	0.3%	-0.0 (-0.1 to 0.1)	1.00 (0.64 to 1.55)	0.9888
Stroke	60	0.4%	69	0.5%	-0.1 (-0.2 to 0.1)	0.87 (0.61 to 1.22)	0.4127
Heart Failure	61	0.4%	98	0.7%	-0.3 (-0.4 to -0.1)	0.62 (0.45 to 0.85)	0.0032
Cardiovascular death	35	0.2%	58	0.4%	-0.2 (-0.3 to -0.0)	0.60 (0.40 to 0.92)	0.0176
Composite safety outcome	521	3.8%	406	2.9%	0.9 (0.4 to 1.3)	1.30 (1.14 to 1.48)	0.0001
Hypotension	110	0.8%	66	0.5%	0.3 (0.1 to 0.5)	1.67 (1.23 to 2.26)	0.0010
Syncope	107	0.7%	80	0.6%	0.2 (0.0 to 0.4)	1.34 (1.00 to 1.79)	0.0497
Bradycardia	87	0.6%	73	0.5%	0.1 (-0.1 to 0.3)	1.19 (0.87 to 1.62)	0.2761
Electrolyte abnormality	144	1.0%	107	0.7%	0.3 (0.0 to 0.5)	1.35 (1.05 to 1.73)	0.0196
Injurious fall	105	0.7%	110	0.8%	-0.0 (-0.2 to 0.2)	0.95 (0.73 to 1.24)	0.7129
AKI or acute renal failure	193	1.3%	117	0.8%	0.5 (0.3 to 0.8)	1.66 (1.32 to 2.08)	0.0000

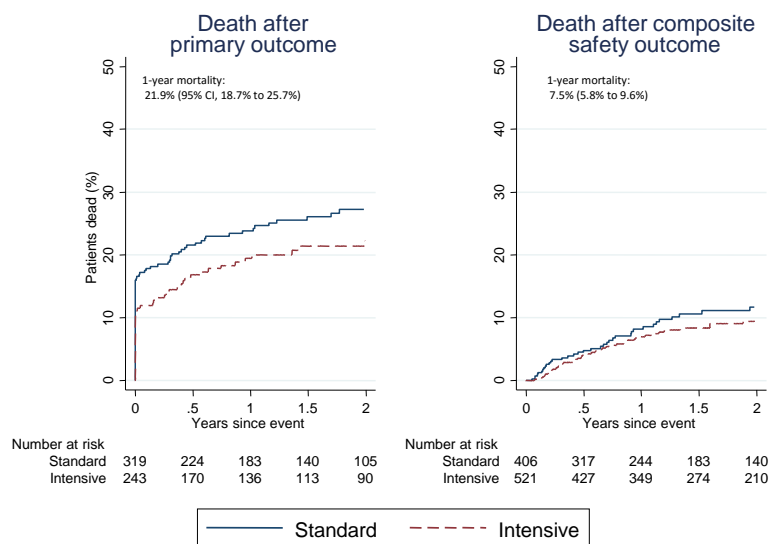
Table 23: Risk ratios for covariates selected for the risk prediction models

Characteristic	Primary outcome		Composite safety outcome	
	Risk ratio (95% CI)	P-value	Risk ratio (95% CI)	P-value
Intensive therapy	0.74 (0.62 to 0.88)	0.0005	1.29 (1.13 to 1.47)	0.0002
Age (per 5 years higher)	1.24 (1.18 to 1.31)	<0.0001	1.25 (1.20 to 1.30)	<0.0001
Log albumin creatinine ratio (per doubling)	1.19 (1.14 to 1.24)	<0.0001	1.15 (1.11 to 1.19)	<0.0001
Sub-clinical CVD	2.16 (1.81 to 2.59)	<0.0001	1.42 (1.21 to 1.66)	<0.0001
Number of anti-hypertensive agents	1.12 (1.03 to 1.21)	0.0099	1.14 (1.07 to 1.22)	0.0001
Current smoker	1.81 (1.41 to 2.31)	<0.0001	1.59 (1.30 to 1.95)	<0.0001
Log serum creatinine (per doubling)	1.29 (1.05 to 1.57)	0.0130	1.28 (1.01 to 1.64)	0.0414
Log triglycerides (per doubling)	1.25 (1.11 to 1.41)	0.0002		
Sub-clinical CKD			1.30 (1.05 to 1.60)	0.0141
Female sex			1.17 (1.00 to 1.36)	0.0550

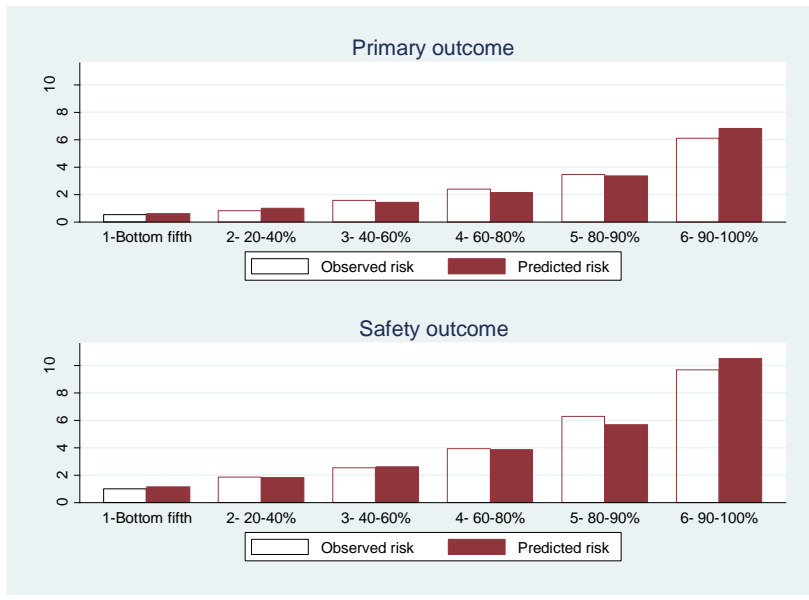
**Figure 1:** Kaplan Meier curves for time to event for primary outcome and composite safety outcome



**Figure 2:** Kaplan Meier plots of time to death following a) primary outcome, b) safety outcome

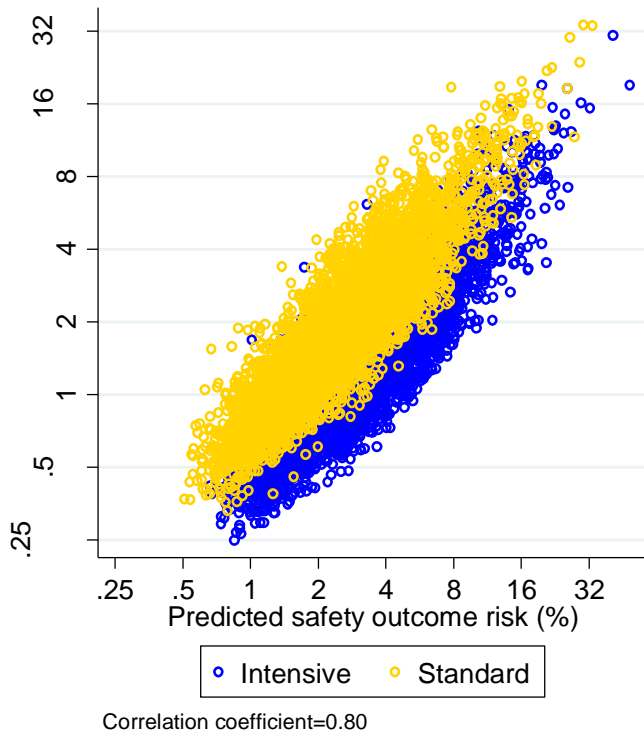


**Figure 35:** Predicted and observed risk by 6 categories of predicted risk



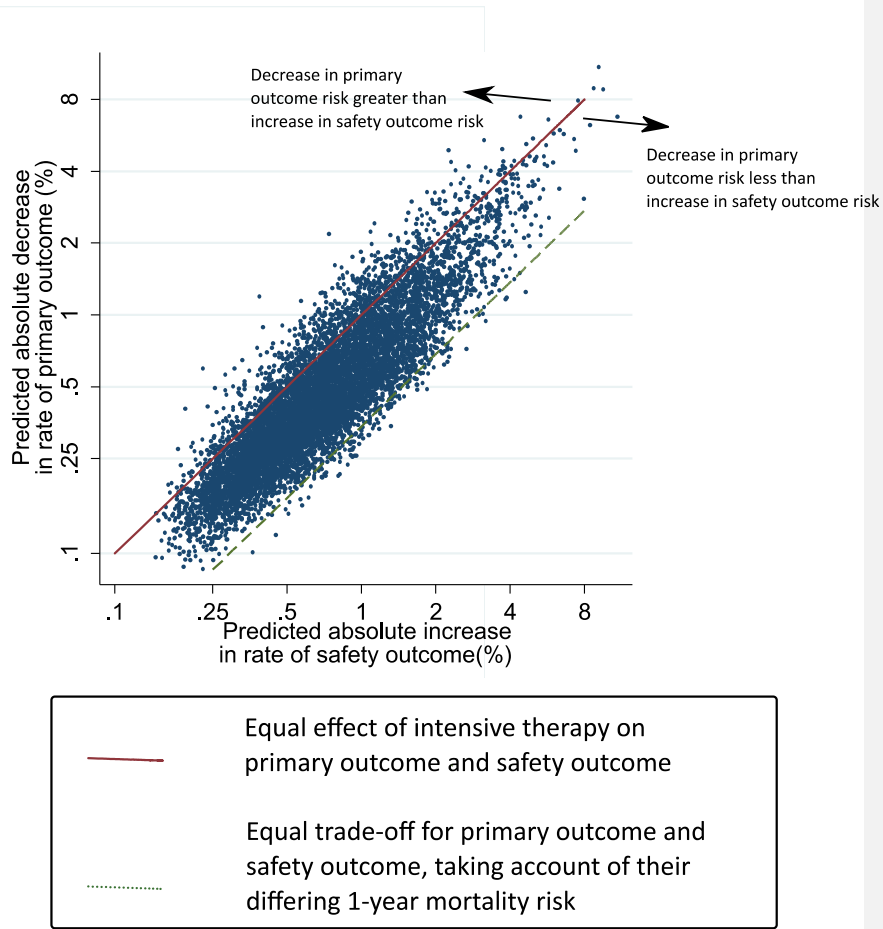
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**Figure 14:** Predicted annual event rate for primary outcome and composite safety outcome





**Figure 45.** Individual patient trade-off between the [predicted 3-year annual](#) increase in primary [efficacy](#) outcome risk, and the predicted decrease in [composite](#) safety outcome risk when using intensive therapy vs standard therapy.



**Figure 51:** Predicted and observed risk by 6 categories of predicted risk



## Bibliography

1. Ioannidis, J. P.; Evans, S. J.; Gotzsche, P. C.; O'Neill, R. T.; Altman, D. G.; Schulz, K.; Moher, D., Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* **2004**, *141* (10), 781-8.
2. Pocock, S. J.; Stone, G. W., The Primary Outcome Is Positive - Is That Good Enough? *N Engl J Med* **2016**, *375* (10), 971-9.
3. Wright, J. T., Jr.; Williamson, J. D.; Whelton, P. K.; Snyder, J. K.; Sink, K. M.; Rocco, M. V.; Reboussin, D. M.; Rahman, M.; Oparil, S.; Lewis, C. E.; Kimmel, P. L.; Johnson, K. C.; Goff, D. C., Jr.; Fine, L. J.; Cutler, J. A.; Cushman, W. C.; Cheung, A. K.; Ambrosius, W. T., A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* **2015**, *373* (22), 2103-16.
4. Ambrosius, W. T.; Sink, K. M.; Foy, C. G.; Berlowitz, D. R.; Cheung, A. K.; Cushman, W. C.; Fine, L. J.; Goff, D. C., Jr.; Johnson, K. C.; Killeen, A. A.; Lewis, C. E.; Oparil, S.; Reboussin, D. M.; Rocco, M. V.; Snyder, J. K.; Williamson, J. D.; Wright, J. T., Jr.; Whelton, P. K., The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials* **2014**, *11* (5), 532-46.
5. Chobanian, A. V.; Bakris, G. L.; Black, H. R.; Cushman, W. C.; Green, L. A.; Izzo, J. L., Jr.; Jones, D. W.; Materson, B. J.; Oparil, S.; Wright, J. T., Jr.; Roccella, E. J., The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *Jama* **2003**, *289* (19), 2560-72.