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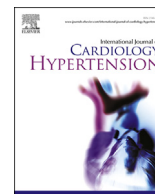
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Research Paper

Use of advanced statistical techniques to predict all-cause mortality in the Systolic Blood Pressure Intervention Trial



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ABSTRACT

Background: The Systolic Blood Pressure Intervention Trial (SPRINT) was conducted in patients with hypertension and additional risk for cardiovascular disease who were randomized to the intensive blood pressure group targeting systolic blood pressure (SBP) less than 120 mm Hg and to the standard group where the target was less than 140 mm Hg. Analyses were done in the matched group of participants with the same gender, same age (± 2 years) and same SBP (± 3 mm Hg) at three months of treatment regardless of initial randomization to intensive or standard group (shaded area in Figure 1).

Methods and results: During 3.26 years of follow-up, intensive group participants had 14.8 mm Hg lower SBP and received on average one more (2.8 vs. 1.8) blood pressure lowering medications. This was associated with lower all-cause mortality in the intensive treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90, $p = 0.003$). The effect on SBP was achieved at 3 months and remained unchanged thereafter. This paper addresses two questions with respect to all-cause mortality in SPRINT in the matched set. 1) What is the effect of receiving more than one drug on all-cause mortality. Conditional logistic regression for all-cause mortality with respect to number of drugs indicated that during the 3.26 years of follow-up persons who received more than one drug were more likely to die (coefficient = 0.5039, OR = 1.6552, $p = 0.0322$) than patients who received one drug. 2) Was there a U curve relationship between on treatment SBP and all-cause mortality? A U curve fitting a quadratic equation (parabola) of SBP and all-cause death was observed. This was seen in the patients randomized to the standard target group in unadjusted analyses as well as in analyses adjusted for demographics or all covariates ($p < 0.001$ for all). The U curves in the combined group and the intensive treatment group were less pronounced.

Conclusion: SPRINT participants who were matched for gender, age, and SBP at 3 months, and received more than one drug had higher all-cause mortality during the 3.26 years of follow-up. Those who were randomized to standard treatment target had a U curve relationship between SBP at three months and all-cause mortality. The U curves in the combined group and the intensive treatment group were less pronounced.

1. Introduction

Hypertension is the leading preventable cause of premature death worldwide [1] and directly increases risk of cardiovascular mortality [2, 3]. Systolic blood pressure (SBP) is an independent risk predictor for stroke, heart failure, and coronary events [4–6]. The Systolic Blood Pressure Intervention Trial (SPRINT) showed that lowering systolic blood pressure to a target of less than 120 mm Hg compared to 140 mm Hg resulted in lower rates of mortality and nonfatal cardiovascular events

[3] as well as all-cause mortality. Other factors such as comorbidities, demographics and visit to visit variability and low adherence may affect mortality of patients with hypertension [7–10]. In SPRINT, patients were randomized to a target SBP of 120 mm Hg or 140 mm Hg. Participants were seen every month for the first three months and every month thereafter. Dose adjustments were based on an average of three blood pressure measurements during the office visit after the patient was seated for 5 minutes when antihypertensive regimens were adjusted based on the study group assignment. The primary composite outcome included

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myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure or death from any cause. The outcome examined in this paper is death from any cause.

The first objective of this paper was to examine whether SPRINT participants who required more than one drug to achieve a given SBP at three months had higher mortality than those requiring only one drug.

The second objective was to examine whether there were U curves in the relationship of SBP at three months and death from any cause. A U curve is a graphical representation of a relationship between risk and outcome where, if the risk factor is at an optimum level the likelihood of an adverse outcome, in this case death, is lowest and increases on either side of the nadir. It was first reported by Stewart in 1979 who in a survey of 169 patients with hypertension observed that the relative risk of myocardial infarction in patients with DBP below 90 mm Hg was about 5 times as high than in patients with DBP 100–109 mm Hg ($p < 0.01$) [11]. Since the introduction of the concept of a physiological optimum, U or J curve relationships have been observed in risk-outcome models of alcohol with all-cause mortality [12], systolic and diastolic blood pressure with cardiovascular outcomes [13,14] and serum potassium with mortality in chronic heart failure [15].

The purpose of this study is to report on whether receiving more than one drug to achieve the same blood pressure at follow up is associated with increased all-cause mortality in SPRINT and to examine whether U curve relationships exist between on treatment and all-cause mortality.

2. Methods

SPRINT was a randomized, controlled, open-label trial, in 102 participating study locations on patients who were at least 50 years old, had SBP of 130–180 mm Hg, and had an increased risk of cardiovascular events. Increased cardiovascular risk was defined by one or more of the following: clinical or subclinical cardiovascular disease other than stroke, chronic kidney disease with eGFR of 20 to less than 60 ml/min per 1.73 m² BSA 10-year risk of cardiovascular disease of 15% or greater on the basis of the Framingham risk score and age of 75 years or older. Patients with diabetes, prior stroke, congestive heart failure with symptoms or ejection fraction less than 35%, proteinuria over 1 g per day, or problems with medication adherence were excluded. Demographic data were collected at baseline and clinical and laboratory data were collected at baseline and subsequently every 3 months.

Participants were assigned to a standard-treatment group with blood pressure target of less than 140 mm Hg or an intensive-treatment group with a target of less than 120 mm Hg. This resulted in three subsets of participants as shown in Fig. 1: those randomized to the intensive SBP target of less than 120 mm Hg (left), those randomized to the standard SBP target of less than 140 mm Hg (right) and the intersection or matched group that included participants who had the same gender, same age (± 2 years) and same SBP (± 3 mm Hg) at three months of treatment regardless of randomization to intensive or standard group. Among the 8919 SPRINT patients with complete data, the matched group included 5814 patients (2907 pairs) who achieved similar SBP (± 3 mm Hg) at 3 months of treatment regardless of randomization to intensive or standard treatment. At 1 year, the mean SBP was 121.4 mm Hg in the intensive treatment group and 136.2 mm Hg in the standard treatment group. The effect on SBP was achieved at 3 months and remained unchanged thereafter. All-cause mortality, the focus of this paper, was significantly lower in the intensive treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90; $p = 0.003$). This analysis was performed by the SPRINT study investigators.

Statistical analyses pertaining to J and U curves were performed by a method reported by Amarantunga and Cabrera in 2015. They examined the presence of linear trends versus nonlinear trends such as U curves or J curves by fitting incrementally linear, quadratic and tricubic equations to the data. U curves or quadratic curves are second order polynomials where both branches are symmetric. On the other hand, J curves are

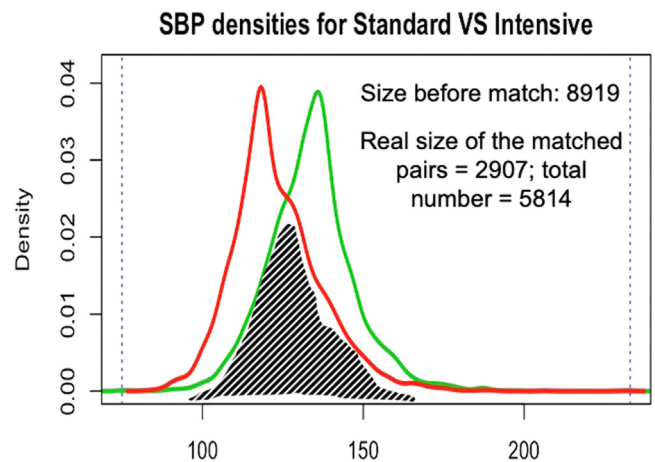


Fig. 1. Distribution on the left (red) pertains to patients randomized to the intensive target group. Distribution on the right (green) pertains to patients randomized to the standard target group. Shaded area in black represents patients who had the same gender, systolic blood pressure ± 3 mm Hg and age ± 2 years, at three months regardless of whether they were initially randomized to the intensive target group or to the standard target group. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

cubic splines with one knot at the median of the X variable [17]. J curves are suitable when the relationship is not symmetric. The fitting method used for these relationships is incremental, starting with a linear fit then adding a quadratic term and then adding the cubic spline term also called tricubic. To decide between a U curve and a J curve we compared the p-value of the U curve to the p-value of the J curve. If the p-value of the U curve was higher than the p-value of the J curve, the relationship is quadratic or U shaped. If the opposite is true, the relationship is J shaped. The outputs of these equations include confidence intervals and p-values [16].

This method works for linear regression models, logistic regression models and Cox proportional hazard models. The response (Y) could be a numeric response (SBP) or binary (dead or alive) or time to event (time to death). In the logistic model the response gets translated to a response such as $\text{logit}(\text{Prob}(\text{Dead}))$ (where $\text{logit}(p) = \log(p/(1-p))$), in the survival model the response is the $\log(\text{hazard ratio})$.

The U-shaped model is given by the equation $\text{Response} = \text{linear} + \text{quadratic term}$, The J-shaped model is $\text{Resp} = \text{linear} + \text{quadratic} + \text{tri-cubic}$.

The tri-cubic term is written as $(\text{SBP} - \text{SBP}_0)_+^3$, which means equals to $(\text{SBP} - \text{SBP}_0)^3$ if $\text{SBP} > \text{SBP}_0$ and 0 if $\text{SBP} \leq \text{SBP}_0$. We chose SBP_0 as the median SBP.

We tested the difference between the quadratic and cubic models by using a likelihood ratio chi-square test.

This paper addresses two questions with respect to all-cause mortality in the matched group of SPRINT participants. 1) What was the effect of receiving more than one drug on all-cause mortality. 2) Was there a U curve relationship between on treatment SBP and all-cause mortality in the matched, standard, and intensive target groups.

This paper aims to answer 2 questions with respect to all-cause mortality:

1. What is the effect of receiving more than one drug to achieve the same SBP at three months on all-cause mortality compared to those using one drug in SPRINT? Conditional logistic regression, a standard modeling procedure for matched pairs [18], for all-cause mortality with respect to number of drugs was performed. The observations were stratified by one-to-one matched pairs, as explained earlier in this section, and the number of drugs was coded by an indicator

variable taking value 1 for more than one drug vs value 0 for one or no drugs.

2. Are there U curve relationships between on treatment SBP and all-cause mortality in the standard and intensive groups of SPRINT? Following the procedure for detecting U and J curves outlined in the paragraph above, we investigated the presence and configuration of U-curves in the matched set, the standard SBP target group and the intensive target group.

3. Results

During the 3.26 years of follow-up, intensive group participants had 14.8 mm Hg lower SBP and received on average one more (2.8 vs. 1.8, mean: 2.631, SD 1.029 vs. 1.826, SD 1.052) blood pressure lowering medications. These data are consonant with current literature on these medications. This was associated with lower all-cause mortality in the intensive treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90, $p = 0.003$). These analyses were performed by the SPRINT study investigators. There were only 489 patients who at randomization were on monotherapy and who remained on monotherapy until the end of the third month visit. This analysis was performed by the investigators of this paper. In these patients, the days from randomization were mean 96 days, median 93 days, lower quartile 91 days, higher quartile 101 days, minimum 76 days and maximum 139 days. Four patients died (two from cardiovascular causes) before the end of the three months. The times of death were at 34, 52, 70 and 88 days. This did not allow formal survival analysis in this subset. This analysis was performed by the investigators of this paper. Cardiovascular mortality was not significantly higher in patients receiving more than one drug compared to those who received only one drug and the time was at three months (OR = 2.4, 95% CI 0.8455-6.812, $p = 0.1$). The characteristics of the matched group are reported in Table 1.

This analysis was performed by investigators of the present paper who used data from SPRINT. In the matched group, persons who received more than one drug were more likely to die (coefficient = 0.5039, OR = 1.6552, 95% CI 1.044-2.624, $p = 0.032$). The proportion of subjects who died was correlated to the baseline DBP, SBP and pulse pressure. In the standard treatment group, a U curve of SBP and all-cause death was observed in unadjusted analyses as well as for analyses adjusted for demographics or all covariates ($p < 0.001$ for all (Fig. 2). The U curves in the combined group (Fig. 3) and the intensive treatment group were less pronounced ($p = 0.26$ and 0.43 respectively). Patients with low SBP were more likely to be Hispanic, with history of cardiovascular disease, and to take a statin. Patients with high SBP were more likely to be black, have higher Framingham risk score and higher LDL. In the matched group the U curve was evident but of borderline statistical significance (Fig. 3 $p = 0.26$) and a statistically significant U curve effect was not observed in the intensive treatment group.

4. Discussion

In this study of SPRINT participants who had the same blood pressure at 3 months of therapy, persons who received more than one drug were more likely to die. This finding is consistent with the fact that the Framingham Risk Score assigns a point to those receiving antihypertensive therapy. Administration of more than one drug may lead to more blood pressure variability throughout the day as well as lower adherence an important cause of uncontrolled or resistant hypertension.

A J curve of SBP and all-cause death was observed in unadjusted analyses as well as for analyses adjusted for demographics or all covariates in the standard treatment group ($p < 0.001$ for all, (Fig. 2) while in the matched group the U curve was evident but of borderline statistical significance (Fig. 3, $p = 0.26$) and a statistically significant U curve was not observed in the intensive treatment group.

Limitations of this study include that it is a post hoc analysis of data collected in SPRINT that did not include patients with diabetes, patients

Table 1
Characteristics of the matched group.

Characteristic	Intensive treatment group (n = 2907)	Standard treatment group (n = 2907)	p value
After matching			
Age – yr ^a			
Overall	68.1 ± 9.3	68.1 ± 9.4	0.9944
Among those ≥ 75 yr of age	79.7 ± 3.8	79.6 ± 3.8	0.9026
Male gender – no. (%) ^a	1897 (65.3)	1897 (65.3)	1
SBP at 3 months — mm Hg ^a	128.9 ± 12.6	129.4 ± 12.6	0.0979
DBP at 3 months — mm Hg	71.5 ± 10.8	72.8 ± 10.9	<0.0001
Requiring >1 drug at 3 months – no. (%)	2597 (89.3)	1622 (55.8)	<0.0001
Criterion for increased cardiovascular risk — no. (%)			
Age ≥75 yr	855 (29.4)	857 (29.5)	0.977
Chronic kidney disease	839 (28.9)	815 (28)	0.5038
Cardiovascular disease	567 (19.5)	572 (19.7)	0.8948
Clinical	465 (16)	488 (16.8)	0.4358
Subclinical	151 (5.2)	143 (4.9)	0.6752
Framingham 10-yr cardiovascular disease risk score ≥15%	1852 (64)	1774 (61.3)	0.0430
Race or ethnic group			0.3803
Non-Hispanic black	860 (29.6)	874 (30.1)	
Hispanic	284 (9.8)	279 (9.6)	
Non-Hispanic white	1698 (58.4)	1707 (58.7)	
Other	65 (2.2)	47 (1.6)	
Black race	904 (31.1)	917 (31.5)	0.7344
Baseline SBP — mm Hg	141 ± 15.8	138.7 ± 15	<0.0001
Baseline DBP — mm Hg	78.3 ± 12.2	77.7 ± 11.8	0.05622
Serum creatinine — mg/dl	1.08 ± 0.34	1.08 ± 0.34	0.737
Estimated GFR — ml/min/1.73 m ²			
Among all participants	71.8 ± 20.9	71.5 ± 20.3	0.5238
Among those with estimated GFR ≥60 ml/min/1.73 m ²	81.6 ± 15.7	80.8 ± 15.1	0.1067
Among those with estimated GFR <60 ml/min/1.73 m ²	47.8 ± 9.3	47.6 ± 9.5	0.6317
Ratio of urinary albumin (mg) to creatinine (g)	44.5 ± 173.8	38.3 ± 145.6	0.1457
Fasting total cholesterol — mg/dl	189.9 ± 41	189.5 ± 40.9	0.6661
Fasting HDL cholesterol — mg/dl	53 ± 14.6	52.8 ± 14.3	0.4324
Fasting total triglycerides — mg/dl	124.4 ± 88.1	125.6 ± 80.5	0.57
Fasting plasma glucose — mg/dl	99 ± 13.6	98.7 ± 12.8	0.4009
Statin use — no./total no. (%)	1215/2888 (42.1)	1342/2889 (46.5)	0.0009
Aspirin use — no./total no. (%)	1508/2901 (52)	1494/2902 (51.5)	0.7225
Smoking status — no. (%)			0.2449
Never smoked	1279 (44)	1281 (44.1)	
Former smoker	1226 (42.2)	1273 (43.8)	
Current smoker	399 (13.7)	351 (12.1)	
Missing data	3 (0.1)	2 (0.1)	
Framingham 10-yr cardiovascular disease risk score — %	20.5 ± 10.9	19.8 ± 10.4	0.0083
Body-mass index	29.7 ± 5.6	29.9 ± 5.8	0.1582
Antihypertensive agents — no./patient	1.8 ± 1	1.8 ± 1	0.5367
Not using antihypertensive agents — no. (%)	265 (9.1)	274 (9.4)	0.7175

The p value is obtained from a two-sample t-test (for continuous variables) or a chi-square test (for categorical variables).

^a Variables used for matching.

with prior stroke, those residing in nursing homes or assisted-living facilities. An additional limitation is that precise information on previous (prior to randomization) exposure is not available in the SPRINT database. However, the trial was randomized, included a large sample size with participants of diverse ages, demographics and comorbidities. Also,

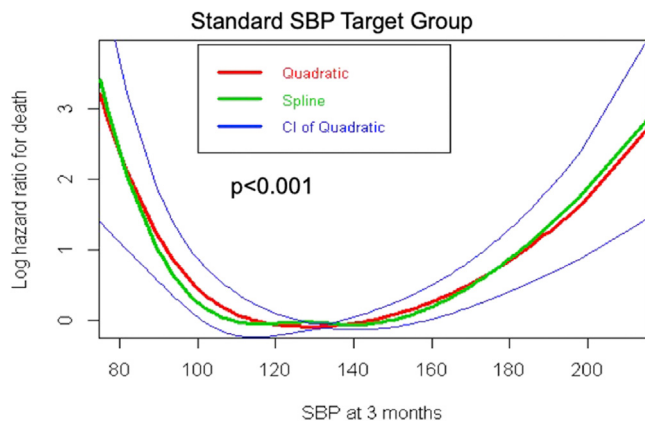


Fig. 2. Risk of death using a quadratic (parabolic) function (red) and a fitted spline (green) indicating a U shaped relationship between systolic blood pressure at 3 months and risk of death ($p < 0.001$). Blue lines correspond to confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

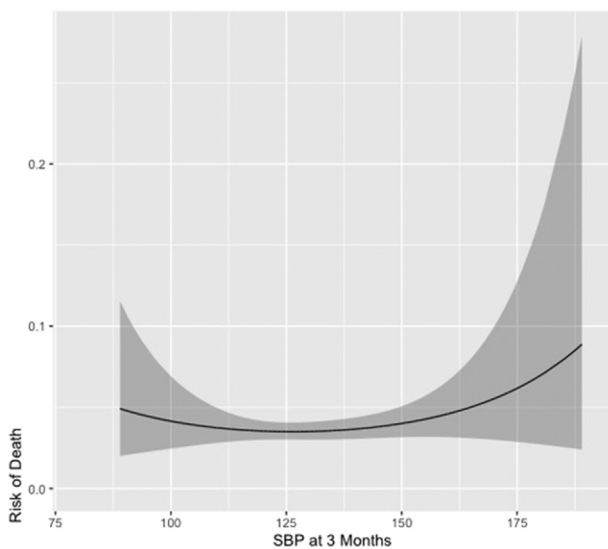


Fig. 3. Risk of death using a quadratic (parabolic) function and confidence intervals (shaded area) indicating a Ushaped relationship between systolic blood pressure at 3 months and risk of death ($p = 0.26$).

it proved an all-cause mortality difference between the two randomized groups.

Our study implies that caution is needed prior to prescribing and administering more than one antihypertensive medication and perhaps when desired blood pressure control is not achieved to make sure that the maximum dose on the first medication is given and to be vigilant regarding elderly patients and patients with comorbidities or other characteristics that put them on the left side of the U curve [17,18]. Adherence to medications is important, as more blood pressure medications may be added unnecessarily with nonadherence, increasing the burden of unwanted side effects. Polypharmacy or inappropriate dosing may cause cognitive and mental status changes especially in the elderly, due to decreased cerebral perfusion, along with electrolyte imbalance and other cardiovascular events.

It is not clear why a statistically significant U curve relationship was observed in the standard treatment group, but not in the intensive care group. It is possible that the effect was attenuated because of the lower SBP in this group with lower signal to noise ratio. Sobieraj et al. examining the SPRINT database reported that there were adverse effects or a

curve low on-treatment diastolic blood pressure on cardiovascular risk in the SPRINT population and that after adjusting for covariates, low diastolic blood pressure showed no significant effects on cardiovascular risk [19,20,21]. These authors did not report on all-cause mortality.

5. Conclusion

SPRINT participants who required more than one drug to achieve the same SBP at three months had higher all-cause mortality compared to those who received only one drug. A statistically significant U curve relationship between SBP at three months and all-cause mortality was observed in patients randomized to the standard target group. Those who were randomized to standard treatment target had a U curve relationship between SBP at three months and all-cause mortality. The U curves in the combined group and the intensive treatment group were less pronounced.

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CRediT authorship contribution statement

William J. Kostis: Conceptualization, Writing - original draft. **Javier Cabrera:** Formal analysis. **John B. Kostis:** Project administration, Writing - review & editing. **Jennifer Wellings:** Writing - review & editing. **Stavros Zinonos:** Formal analysis. **Jeanne M. Dobrzynski:** Writing - review & editing. **Daniel Blickstein:** Data curation, Formal analysis.

Declaration of competing interest

The authors declare that they have no competing interests.

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