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Impact of Cardiovascular Risk on the Relative Benefit and Harm of Intensive Treatment of Hypertension

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ABSTRACT

BACKGROUND The lower rate of primary outcome events in the intensive treatment group in SPRINT (Systolic Pressure Intervention Trial) was associated with increased clinically significant serious adverse events (SAEs). In 2017, the American College of Cardiology and American Heart Association issued risk-based blood pressure treatment guidelines. The authors hypothesized that stratification of the SPRINT population by degree of future cardiovascular disease (CVD) risk might identify a group which could benefit the most from intensive treatment.

OBJECTIVES This study investigated the effect of baseline 10-year CVD risk on primary outcome events and all-cause SAEs in SPRINT.

METHODS Stratifying by quartiles of baseline 10-year CVD risk, Cox proportional hazards models were used to examine the associations of treatment group with the primary outcome events and SAEs. Using multiplicative Poisson regression, a predictive model was developed to determine the benefit-to-harm ratio as a function of CVD risk.

RESULTS Within each quartile, there was a lower rate of primary outcome events in the intensive treatment group, with no differences in all-cause SAEs. From the first to fourth quartiles, the number needed to treat to prevent primary outcomes decreased from 91 to 38. The number needed to harm for all-cause SAEs increased from 62 to 250. The predictive model demonstrated significantly increasing benefit-to-harm ratios (± SE) of 0.50 ± 0.15, 0.78 ± 0.26, 2.13 ± 0.73, and 4.80 ± 1.86, for the first, second, third, and fourth quartile, respectively (p for trend <0.001). All possible pairwise comparisons of between-quartile mean values of benefit-to-harm ratios were significantly different ($p < 0.001$).

CONCLUSIONS In SPRINT, those with lower baseline CVD risk had more harm than benefit from intensive treatment, whereas those with higher risk had more benefit. With 2017 American College of Cardiology/American Heart Association blood pressure treatment guidelines, this analysis may help providers and patients make decisions regarding the intensity of blood pressure treatment. (J Am Coll Cardiol 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

The SPRINT (Systolic Pressure Intervention Trial) tested the hypothesis that treatment to a systolic blood pressure (SBP) goal <120 mm Hg (intensive treatment) in patients ≥50 years of age at high risk for cardiovascular events (without diabetes) was superior to an SBP treatment goal <140 mm Hg (standard treatment) (1). The primary outcome was a composite of myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute compensated heart failure, or death from cardiovascular causes. Over the 3.26 years of follow-up, those randomized to the intensive-treatment arm had a mean achieved SBP of 121.5 mm Hg, whereas those in the standard-treatment arm had a mean achieved SBP of 134.6 mm Hg (1). Compared to those in the

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ABBREVIATIONS AND ACRONYMS

AAFP = American Academy of Family Physicians

ACC = American College of Cardiology

ACP = American College of Physicians

AHA = American Heart Association

CVD = cardiovascular disease

JNC8 = Eighth Joint National Committee

NNH = number needed to harm

NNT = number needed to treat

SAE = serious adverse event

SBP = systolic blood pressure

standard-treatment arm, those in the intensive-treatment arm had a 25% lower incidence of the primary outcome events ($p < 0.001$) and a 27% reduction in all-cause mortality ($p = 0.003$) (1). The number needed to treat (NNT) was 61 to prevent 1 primary cardiovascular outcome and was 90 to prevent 1 death (1). The intensive treatment was equally effective in those who were 75 years of age or older (2).

Largely based on the results of SPRINT, the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (hereafter referred to as the 2017 ACC/AHA blood pressure guidelines) has recommended intensive treatment in SPRINT-eligible patients (3). If this recommendation is implemented in SPRINT-eligible adults, it is estimated that 107,500 deaths could be averted annually in the United States (4). The majority of averted deaths, 67,300 per year, would occur in those ≥75 years of age because of the high event rate in this group. Intensive treatment is projected to prevent 32,700 deaths annually among those with chronic kidney disease and to prevent 46,100 cases of heart failure (4). The downside of intensive compared with standard treatment is an additional 56,100 episodes of hypotension, 34,400 episodes of syncope, 43,400 episodes of electrolyte abnormalities, and 88,700 cases of acute renal injury or acute renal failure (4).

Clinicians and patients are therefore faced with a dilemma. Although there is significant reduction in cardiovascular events and death from intensive treatment, it may be accompanied by additional, clinically significant serious adverse events (SAEs). While the 2017 ACC/AHA blood pressure guidelines recommend intensive treatment for all SPRINT-eligible patients, strategies to identify those who might achieve greater benefit than harm from intensive treatment might be useful. Using probability of the risk for a future cardiovascular event to guide blood pressure management is an emerging paradigm (3,4). We hypothesized that stratification of the SPRINT population by degree of future cardiovascular disease (CVD) risk might identify a group who could benefit the most from intensive treatment, with the least amount of harm from SAEs.

METHODS

DATA ACQUISITION AND HUMAN SUBJECTS. We obtained the SPRINT database through a data use agreement with the *New England Journal of Medicine*, as part of their SPRINT Data Analysis Challenge (5). As an analysis of existing and de-identified data, the Bridgeport Hospital Internal Review Board (Yale New Haven Health) and the Houston Methodist Research Institute Internal Review Board exempted the study from approval.

STATISTICAL ANALYSIS. Subject-specific estimates of the 10-year ACC/AHA CVD risk were determined using the risk prediction equations from the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (6). The SPRINT population was then stratified into quartiles based on 10-year CVD risk. Baseline demographics, risk factors, and achieved SBP between standard and intensive treatment were calculated as mean ± SD for continuous variables and number (percentage) for categorical variables. Tests for trend across quartiles of 10-year CVD risk were conducted by modeling the quartiles as a continuous variable in linear regression models for continuous variables and the Cochran-Armitage test for trend for categorical variables. Cox proportional hazards regression was used to determine treatment hazard ratios for SPRINT primary outcome events, all-cause mortality, and SAEs within each risk quartile. The proportionality assumption of the Cox model was assessed, and there was no evidence for the violation of this assumption. A sensitivity analysis was also performed for this risk stratification after removing those patients with clinical or subclinical CVD. We calculated the following parameters: relative risk reduction, absolute risk reduction, NNT, absolute SAE risk increase, and number needed to harm (NNH).

Following the original design of SPRINT, SAEs were defined as events that were fatal or life-threatening, resulted in disability, led to or prolonged hospitalization, or were judged by investigators to represent a significant hazard or harm to the individual (1). Conditions of interest included hypotension, syncope, bradycardia, electrolyte abnormalities, injurious falls, and acute kidney injury or acute renal failure.

PREDICTIVE MODEL. A predictive model was developed to determine the benefit-to-harm ratio as a function of 10-year CVD risk quartile for SPRINT participants. In this model, we used all-cause SAEs as a robust measure of harm. To develop this predictive model, we employed multiplicative Poisson regression (7) to obtain the average quartile-specific number of predicted events from 4 models: standard treatment using primary outcome events and person-days; standard treatment using all-cause SAEs and SAE-days; intensive treatment using primary outcome