Body Mass Index, Intensive Blood Pressure Management, and Cardiovascular Events in the SPRINT Trial

Oxlund, Christina Stolzenburg; Pareek, Manan; Rasmussen, Benjamin Schnack Brandt; Vaduganathan, Muthiah; Biering-Sørensen, Tor; Byrne, Christina; Almarzooq, Zaid; Olsen, Michael Hecht; Bhatt, Deepak L

Published in:
The American Journal of Medicine

DOI:
10.1016/j.amjmed.2019.01.024

Publication date:
2019

Document version
Accepted manuscript

Document license
CC BY-NC-ND

Citation for published version (APA):
Body Mass Index, Intensive Blood Pressure Management, and Cardiovascular Events in the Systolic Blood Pressure Intervention Trial (SPRINT)

Running Head: Body Mass Index and Cardiovascular Events

Christina Stolzenburg Oxlund, MD, PhD1*; Manan Pareek, MD, PhD2*; Benjamin Schnack Brandt Rasmussen, MD, PhD3; Muthiah Vaduganathan, MD, MPH2; Tor Biering-Sørensen, MD, MPH, PhD2; Christina Byrne, MD, PhD4; Zaid Almarzooq, MD2; Michael Hecht Olsen, MD, PhD, DMSc5; Deepak L. Bhatt, MD, MPH2

1Department of Cardiology, Odense University Hospital, Odense, Denmark
2Brigham and Women’s Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA, USA
3Department of Radiology, Odense University Hospital, Odense, Denmark
4Department of Cardiology, The Heart Centre, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark
5Cardiology Section, Department of Internal Medicine, Holbaek Hospital, Holbaek, Denmark

*Drs. Oxlund and Pareek contributed equally as co-first authors.

Authorship Statement: All authors had access to the data and a role in writing the manuscript.

Funding Source: SPRINT was supported by the National Heart, Lung, and Blood Institute. This exploratory analysis was unfunded.
Disclosures: Dr. Manan Pareek discloses the following relationships – Advisory Board: AstraZeneca; Speaker’s Fee: AstraZeneca and Bayer.

Dr. Muthiah Vaduganathan is supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst | The Harvard Clinical and Translational Science Center (NIH/NCATS Award UL 1TR002541), and serves on advisory boards for AstraZeneca, Bayer AG, and Baxter Healthcare.

Dr. Michael Hecht Olsen discloses that he has received a part-time clinical research grant from the Danish Diabetes Academy supported by the Novo Nordisk Foundation.

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today’s
Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda.

The other authors have no disclosures to report.

**Article Type:** Clinical Research Article

**Key Words:** blood pressure; body mass index; hypertension; safety

**Word Count:** 1,297

**Tables:** 1

**Figure:** 2
Address for Correspondence: Deepak L. Bhatt, MD, MPH; Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School; 75 Francis St, Boston, MA, 02115; Tel: (857) 307-1992; Fax: (857) 307-1955; E-mail: dlbhattmd@post.harvard.edu
ABSTRACT

**Background:** It is unclear whether intensive blood pressure management is well-tolerated and affects risk uniformly across the body mass index (BMI) spectrum.

**Methods:** The randomized, controlled Systolic Blood Pressure Intervention Trial (SPRINT) included 9,361 individuals ≥50 years at high cardiovascular risk, without diabetes mellitus, and a systolic blood pressure 130-180 mmHg. Participants were randomized to intensive versus standard antihypertensive treatment and evaluated for the primary composite efficacy endpoint of acute coronary syndromes, stroke, heart failure, or cardiovascular death. The primary safety endpoint was serious adverse events. We used restricted cubic splines to determine the relationship between BMI, response to intensive blood pressure lowering, and clinical outcomes in SPRINT.

**Results:** BMI measurements could be calculated for 9,284 (99.2%) individuals. Mean BMI was similar between the two treatment groups (intensive group 29.9±5.8 kg/m² vs. standard group 29.8±5.7 kg/m²; P=0.39). Median follow-up was 3.3 years (range 0-4.8 years). BMI had a significant, J-shaped association with risk of all-cause mortality, stroke, and serious adverse events (P<0.05 for all), but these were no longer significant after accounting for key clinical factors (P>0.05 for all). Intensive blood pressure lowering reduced the primary efficacy endpoint and increased the primary safety endpoint compared with standard targets, consistently across the BMI spectrum (P<0.05).

**Conclusion:** The overall efficacy and safety of intensive blood pressure lowering did not appear to be modified by baseline BMI among high-risk older adults.

**Trial Registration:** SPRINT (Systolic Blood Pressure Intervention Trial); ClinicalTrials.gov Identifier: NCT01206062, https://clinicaltrials.gov/ct2/show/NCT01206062
INTRODUCTION

The burden of obesity has been increasing steadily worldwide, is projected to reach 20% by 2025 (1-3), and already exceeds 35% in many states across the United States (4). Obesity commonly tracks with other cardiometabolic risk factors, including hypertension (5,6), and is associated with manifest cardiovascular disease (7,8). Approximately 7% of deaths worldwide are attributed to overweight or obesity (1). As such, dedicated strategies are needed to reduce cardiovascular risk in the growing subset of patients who are overweight or obese. In the Systolic Blood Pressure Intervention Trial (SPRINT), intensive versus standard blood pressure lowering reduced major adverse cardiovascular events, but with an excess in certain adverse events, among a broad range of high-risk older adults (9). The findings were confirmed in a meta-analysis, and the latest iteration of the US high blood pressure guidelines lowered diagnostic and treatment thresholds for hypertension (10,11). However, physiologic changes in obesity may affect the efficacy and tolerability of intensive blood pressure treatment and result in non-uniform risk modification across the body mass index (BMI) spectrum (12,13). Leveraging data from SPRINT, we explored the relationship between BMI, treatment response to intensive blood pressure lowering, and cardiovascular outcomes among high-risk adults without diabetes mellitus.

METHODS

The rationale, protocol, and primary results of SPRINT have been previously published (9,14). In this randomized, controlled, open-label trial, 9,361 non-diabetic U.S. adults who were least 50 years of age, at high cardiovascular risk, and had a systolic blood pressure between 130-180 mmHg obtained at screening were allocated to receive either intensive or standard antihypertensive treatment (target systolic blood pressures <120mmHg versus <140mmHg). A limited SPRINT dataset is available from the National Heart, Lung, and Blood Institute’s Biologic Specimen and
Data Repository Information Coordinating Center. The institutional review board at Brigham and Women’s Hospital waived approval for use of these data (15,16). We restricted our analysis to individuals in whom a baseline BMI was available. The primary efficacy endpoint was the composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes. Secondary efficacy endpoints comprised the individual components of the primary endpoint (stroke, acute decompensated heart failure, and cardiovascular death) and death from any cause. The primary safety endpoint was composite serious adverse events, i.e., hypotension, syncope, electrolyte abnormalities, acute kidney injury or failure, or injurious falls.

We assessed baseline characteristics stratified by World Health Organization categories of BMI: underweight: <18.5 kg/m², normal weight: 18.5-24.9 kg/m², overweight: 25.0-29.9 kg/m², and obese: ≥30 kg/m² (17). Since only 47 individuals (0.5%) were underweight, they were merged with normal weight subjects. Group-wise comparisons across the three BMI categories were performed with the Wilcoxon-type test for trend (18). The relationship between BMI as a continuous variable and each of the endpoints was evaluated using unadjusted and adjusted restricted cubic spline models. Similar to prior SPRINT-based investigations from our group (15,16), a covariate set for adjustment was defined a priori and included treatment group, age, sex, smoking status, number of antihypertensive agents, history of cardiovascular disease, total cholesterol, high-density lipoprotein cholesterol, serum creatinine, and urine albumin-creatinine ratio. We further examined the effects of intensive versus standard blood pressure lowering across the BMI spectrum using interaction analyses. The number of knots was based on the lowest value of Akaike information criterion. Stata/IC 15 (StataCorp LP, College Station, TX, USA) was used for all analyses.
RESULTS

BMI measurements were obtained for 9,284 of 9,361 (99.2%) individuals enrolled in SPRINT. Of these, 1,729 (18.6%) were underweight or normal weight, 3,599 (38.8%) were overweight, and 3,956 (42.6%) were obese. Mean BMI was similar in the two study groups (intensive treatment group 29.9±5.8 kg/m² vs. standard treatment group 29.8±5.7 kg/m²; P=0.39). Mean age, systolic blood pressure, and the prevalence of current smokers decreased, while diastolic blood pressure, fasting blood glucose, and estimated glomerular filtration rate increased across BMI categories (P<0.001) (Table).

Median follow-up was 3.3 years (range 0-4.8 years), with 561 (6.0%) primary efficacy events and 3,505 (37.8%) primary safety events occurring during study follow-up. Figure 1 shows the continuous relationship between BMI and tested efficacy and safety endpoints. BMI was not significantly associated with the primary efficacy endpoint, death from cardiovascular causes, or heart failure (P>0.05). Furthermore, despite non-linear J-shaped associations with death from any cause, stroke, and serious adverse events (test for overall trend, P<0.05; test for non-linearity versus linearity, P<0.05), none of these remained significant upon multivariable adjustment (P>0.05).

Whether BMI modified the effect of intensive versus standard antihypertensive treatment for each endpoint was tested as a continuous interaction (Figure 2). We found similar treatment effects on nearly all endpoints across the spectrum of BMI values (Pinteraction>0.05 for interaction). There was a significant interaction between treatment randomization and BMI for cardiovascular death, such that the benefit of intensive treatment on death from cardiovascular causes appeared to be greatest in participants with a BMI ~30 kg/m² (P=0.02 for interaction).
DISCUSSION

In this secondary analysis of a randomized controlled trial of non-diabetic individuals at high cardiovascular risk, we observed that BMI was non-linearly associated with the risk of death, stroke, and serious adverse events. However, we did not observe independent cardiovascular risk associated with BMI when accounting for imbalances in traditional risk factors. Furthermore, BMI did not modify the efficacy and safety of intensive antihypertensive treatment except the endpoint of death from cardiovascular causes, for which a particular benefit among individuals with a BMI of ~30 kg/m² was observed.

The relationship between BMI and mortality in individuals with or without certain chronic conditions is J-shaped (1,19-21). However, among patients with established cardiovascular disease, an obesity paradox or reverse epidemiology has been described, questioning that the ideal BMI, conventionally defined as 18.5-24.9 kg/m², signifies the optimal cardiometabolic state (22-25). Indeed, in a recent meta-analysis of observational studies including patients with established hypertension, a BMI of 27.5 to 30 kg/m² was associated with the lowest risk of all-cause mortality and cardiovascular disease (26). However consistent with prior findings (27), apparent differences in cardiovascular risk profiles across the BMI spectrum were accounted for by variation in background risk factors.

Intensive blood pressure lowering also appeared to be safe and effective across the BMI spectrum. In patients with obesity, altered pharmacokinetics and pharmacodynamics may lead to dosing problems that could potentially affect the rate of medication side effects (12,13). These data, however, support that safety of intensive blood pressure lowering was not influenced by baseline BMI. Our analyses confirm and extend the findings of a recent SPRINT-based report (which was limited to the primary efficacy endpoint) (28) to inform a broad range of endpoints. It is
reassuring that two separate working groups using two different analytical approaches reached similar conclusions.

The strengths of this study included the large and well-characterized study population, and the use of robust statistical modeling of BMI as a continuous measure, recognizing the potential for inherent non-linear effects. However, a few limitations of our study should be noted. The analysis was not prespecified and its external validity is unknown. Whether BMI is the best marker for obesity may be questioned as well. Certainly, it is the most widely used worldwide and we used internationally accepted definitions for categorization. However, measures of central adiposity, e.g., waist circumference, waist-hip ratio, and waist-height ratio, may be better in predicting and discriminating disease risk (29,30). Furthermore, we were unable to adjust for other risk factors closely associated with BMI, e.g., diet and physical activity. Lastly, we were unable to examine the effect of body weight fluctuations over time which are also known be associated with greater cardiovascular risk (31,32).

In this SPRINT trial, BMI does not appear to modify the risks and benefits of intensive versus standard antihypertensive treatment. As such, intensive blood pressure lowering may represent an important cardiovascular risk reduction strategy among the growing population of obese persons worldwide.
REFERENCES


ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the
Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of
the American College of Cardiology/American Heart Association Task Force on Clinical Practice

(12) Smit C, De Hoogd S, Bruggemann RJM, et al. Obesity and drug pharmacology: a review of the
influence of obesity on pharmacokinetic and pharmacodynamic parameters. Expert Opin Drug

(13) Esler M, Lambert G, Schlaich M, et al. Obesity Paradox in Hypertension: Is This Because
Sympathetic Activation in Obesity-Hypertension Takes a Benign Form? Hypertension 2018

(14) Ambrosius WT, Sink KM, Foy CG, et al. The design and rationale of a multicenter clinical
trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure

High Blood Pressure Guidelines, and Long-Term Cardiovascular Risk in SPRINT. Am J Med 2018

(16) Pareek M, Vaduganathan M, Biering-Sorensen T, et al. Pulse Pressure, Cardiovascular Events,
and Intensive Blood Pressure Lowering in the Systolic Blood Pressure Intervention Trial (SPRINT).

(17) WHO Expert Consultation. Appropriate body-mass index for Asian populations and its


(19) Global BMI Mortality C, Di Angelantonio E, Bhupathiraju S, et al. Body-mass index and all-
cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four


FIGURES

Figure 1. The association between body mass index and efficacy and safety endpoints.

The solid lines represent the incidence ratio (per 100 person-years) at each body mass index interval. The dashed lines represent the upper and lower bounds of the 95% confidence interval. The bars represent the distribution of body mass index values. The P-values are for unadjusted trends.
Figure 2. The effect of intensive versus standard blood pressure lowering across the spectrum of body mass index values for select clinical endpoints.

The solid black lines represent unity (hazard ratio = 1), and the solid blue lines represent the hazard ratio at each body mass index interval. The dashed lines represent the upper and lower bounds of the 95% confidence interval. Abbreviation: BP = blood pressure.