Published in final edited form as:

J Sex Med. 2020 February ; 17(2): 238–248. doi:10.1016/j.jsxm.2019.11.256.

Effect of Intensive vs. Standard Blood Pressure Treatment Upon Erectile Function in Hypertensive Men: findings from the Systolic Blood Pressure Intervention Trial (SPRINT)

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Abstract

Background: The effect of intensive blood pressure control upon erectile function in men with hypertension, but without diabetes, is largely unknown.

Aim: To examine the effects of intensive systolic blood pressure (SBP) lowering on erectile function in a multiethnic clinical trial of men with hypertension.

Methods: We performed subgroup analyses from the Systolic Blood Pressure Intervention Trial (SPRINT; [ClinicalTrials.gov: NCT01206002](https://clinicaltrials.gov/ct2/show/study/NCT01206002), in a sample of 1255 men with hypertension and increased cardiovascular disease risk, ages 50 years or older. Participants were randomly assigned to an intensive treatment group (SBP goal of <120 mmHg) or a standard treatment group (SBP goal of <140 mmHg).

Main Outcome Measures: The main outcome measure was change in erectile function from baseline, using the 5- item International Index of Erectile Function (IIEF-5) total score, and erectile dysfunction (ED; defined as IIEF-5 score $\leq$ 21) after a median follow-up of 3.0 years.

RESULTS: At baseline, roughly two-thirds (66.1%) of the sample had self-reported erectile dysfunction. At 48 months post-randomization, we determined that the effects of more intensive blood pressure lowering were significantly moderated by race/ethnicity (p for interaction = 0.0016), prompting separate analyses stratified by race-ethnicity. In non-Hispanic Whites, participants in the intensive treatment group reported slightly, but significantly better change in IIEF-5 score than those in the standard treatment group (mean difference = 0.67; 95% CI, 0.03, 1.32; $P = 0.041$). In non-Hispanic Blacks, participants in the intensive group reported slightly worse change in IIEF-5 score compared to those in the standard group (mean difference = -1.17; 95% CI - 1.92, -0.41; $p = 0.0025$). However, in non-Hispanic whites and non-Hispanic blacks, further adjustment for baseline IIEF-5 score resulted in non-significant differences ($p > 0.05$) according to treatment group.

In Hispanic/Other participants, there were no significant differences in change in IIEF-5 score between the two treatment groups ($p = 0.40$). In a subgroup of 280 participants who did not report ED at baseline, the incidence of ED did not differ in the two treatments ($p = 0.53$), and was without interaction by race-ethnicity.

CLINICAL IMPLICATIONS: The effect of intensive treatment of blood pressure on erectile function was very small overall, and likely not of great clinical magnitude.

Strengths and Limitations: Although this study included a validated measure of erectile function, testosterone, other androgen, and estrogen levels were not assessed.

Conclusions: In a sample of male patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in statistically significant effects on erectile function that differed according to race-ethnicity, although the clinical importance of the differences may be of small magnitude.

Primary Funding Source: National Institutes of Health.

INTRODUCTION

Sexual activity and function are important components of health-related quality of life (HRQL) throughout the lifespan (1). Sexual dysfunction, defined by the World Health Organization as “the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish” (2) presents a considerable challenge to HRQL, interpersonal relationships, and mood states (3). The condition of erectile dysfunction (ED) in men has gained increased interest in recent years, as it is estimated that ED affects 30 million men in the United States (4), and nearly 150 million men worldwide report some degree of ED (5). The etiology of ED is multifactorial, and ED may be an independent risk factor for cardiovascular disease (CVD) (6).

Several studies have found that ED is highly prevalent in men with hypertension (HTN) (1;7-9). It is acknowledged that increased blood pressure may lead to impaired vascular function throughout the body; thus, it has been postulated that reduced nitric oxide-induced vasodilation, and stenosis of vessels due to atherosclerotic plaques may also contribute to reduced blood flow through penile arteries (8). The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that intensive lowering of systolic blood pressure (SBP) to a goal <120 mm Hg results in reduced non-fatal and fatal CVD events compared to standard treatment of SBP goal <140 mm Hg in adults with HTN (10), that the effect of intensive treatment upon CVD events is similar in racial-ethnic groups (11), and that the two treatments did not differ in components of self-reported health-related quality of life (HRQL) (12). Thus, while it is plausible that lowering blood pressure may have beneficial effects upon erectile function, it is also conceivable that lowering of blood pressure may lead to reduced perfusion, which may negatively influence erectile function. Consequently, the effect of intensive treatment for HTN upon erectile function is unclear. In addition, the role of antihypertensive medications in contributing to, or ameliorating ED remains unclear (13). Also, the association of race/ethnicity and erectile function has not been extensively examined (14), although it is known that the prevalence of risk factors for ED differ across race/ethnicity groups (15;16).

In consideration of these issues, the purpose of this investigation was to compare the effects of the intensive vs. standard systolic blood pressure lowering upon erectile function in men in a subgroup of the large, multi-ethnic SPRINT randomized clinical trial. We hypothesized that men in the intensive treatment would report more favorable erectile function than men in the standard treatment.

METHODS

Trial Design and Oversight

Trial Design and Oversight, and Study Population—The design, eligibility criteria, procedures (17) and primary outcome results (10;18) for SPRINT have been described in detail previously. Briefly, SPRINT was a large, two-armed, multicenter, unmasked randomized clinical trial designed to test whether more intensive treatment of SBP to a goal of <120 mmHg would reduce CVD and unfavorable renal and cognitive outcomes compared to standard SBP treatment to a goal of <140 mmHg in a multi-ethnic sample of 9361 men

and women aged 50 years or older with hypertension and increased cardiovascular risk. Individuals with diabetes, polycystic kidney disease, a prior history of stroke or known dementia were excluded. Enrollment in SPRINT was conducted from November 2010 to March 2013 at 102 clinical sites in the United States, including Puerto Rico. The Institutional Review Board at each clinical site approved the study, and the trial was registered with clinicaltrials.gov (NCT01206062) prior to recruitment. SPRINT also includes several subsamples, including a HRQL subsample consisting of 1987 men and women participants who were selected using a probabilistic algorithm that preserved the randomization blocking and allowed the sampling fraction to vary by clinical site and over time. This investigation involves the 1290 male participants in the SPRINT HRQL subsample.

After randomization, participants were seen monthly for the first 3 months and thereafter every 3 months. All major classes of antihypertensive agents were included in the SPRINT formulary (19), were provided at no cost to the participants, and were assessed at each study visit. Antihypertensive medications for participants in the intensive treatment group were adjusted on a monthly basis to target the SBP goal of <120 mmHg. For participants in the standard treatment group, medications were adjusted to target a SBP of 135 to 139 mmHg. Lifestyle modification was encouraged as part of the management strategy in both treatment groups (10).

On August 20, 2015, after analyses of the primary outcome exceeded the monitoring boundary at two consecutive time points, the Director of the National Heart, Lung and Blood Institute (NHLBI) accepted a recommendation from the independent Data Safety and Monitoring Board to inform investigators and participants of the beneficial cardiovascular outcome results, which prompted the process of terminating the blood pressure lowering intervention per the SPRINT protocol. Thus, this analysis reflects 3.26 years of the originally-planned 5 years of follow-up.

Trial Measures

Outcome Variables

Sexual Activity and Erectile Function.: Sexual activity and erectile function were assessed at baseline, and annually throughout the course of the study. Sexual activity during the previous 4 weeks was assessed by the question, - “Have you engaged in sexual activity of any kind with a partner and/or by yourself (masturbation)?” Participants who answered “yes” then completed questions regarding erectile function during the past 4 weeks, using the 5-item version of International Index of Erectile Function (IIEF-5) questionnaire (20). Previous manuscripts have described the scoring and metric properties of the IIEF-5 (20), and use of the IIEF-5 in SPRINT (21). As suggested by developers of the instrument, ED was operationally defined as a total IIEF-5 score of ≤ 21 (20).

Other Measures—Age, sex, race/ethnicity (non-Hispanic Black(s) [NHB(s)], Hispanic(s) or Others [H/O(s)], non-Hispanic White(s) [NHW(s)]), highest educational attainment (<high school, high school diploma or graduate equivalent degree [GED], post high school, college graduate), living arrangement (alone vs. with other adults), health insurance (yes/

no), alcohol consumption (typical number of drinks/week), and pack-years of smoking were assessed using self-report instruments. In addition, depressive symptoms were assessed via self-report using the Patient Health Questionnaire (PHQ-9) total score (range 0 to 27), with higher scores suggesting more depressive symptoms (22). Cognitive function was assessed via standardized interview using the Montreal Cognitive Assessment (MoCA) total score (range 0 to 30), with higher scores suggesting better cognitive function (23).

At each visit, trained clinical staff measured seated blood pressures with an automated blood pressure device (Omron-HEM-907 XL, Omron Healthcare, Lake Forest, IL, USA) using standardized procedures (10;10;17;24). Blood pressure measurement requirements included measuring blood pressure early during the visit and not following stressful exam components such as blood draws, with proper positioning of the participant in a chair with back support, and proper cuff size determination. The publicly-available Manual of Procedures (MOP) (19) stated that participants should be resting, not completing questionnaires, and not speaking with study staff during the 5-minute rest period or while BP measurements were being taken. The MOP also stated that staff should leave the room during the 5-minute rest period, and provided a script that staff could use to explain that they would be absent during the 5-minute rest period and would then enter the room and obtain the measurements without speaking to the participant.

Additional baseline clinical variables were assessed using standardized procedures, including fasting serum glucose (mg/dl), total cholesterol (mg/dl), and anti-cholesterol medication, or anti-depressant medication. Baseline height and weight were measured using standardized protocols, and baseline Quételet's (body mass) index (BMI) was calculated as weight in kilograms/(height in meters)².

Statistical Analyses—First, we generated descriptive statistics of baseline covariates to characterize the sample, comparing treatment assignment (intensive vs. standard treatment) using the chi-square test for categorical variables and independent Student's t-test for continuous variables.

Thereafter, we used a linear mixed model to examine longitudinal effects of the two treatment groups upon change in IIEF-5 total scores from the baseline value. Fixed effects in the model included treatment group, race/ethnicity, time, and a treatment group by time interaction. The model also included participant-specific and clinic-specific random effects to account for correlation among participants at the same site. We also tested a treatment group by race/ethnicity interaction term, which was highly significant ($p = 0.0016$), supporting subsequent stratification of analyses according to race-ethnicity.

Next, in the subgroup of participants who reported normal erectile function (IIEF-5 score >21) at baseline, we conducted Cox proportional hazards regression to compare incidence of the first report of erectile dysfunction (IIEF-5 score ≤ 21) between the intensive and standard treatment arms. Follow-up time was censored on the date of the last assessment. As there was no evidence for a race-ethnicity interaction in the analyses of incident erectile dysfunction ($p = 0.65$), we report these latter results without race-ethnicity stratification.

The a priori 2-tailed alpha level of significance for all analyses was set at $p = 0.05$. All analyses were conducted at the SPRINT Coordinating Center with the use of SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Descriptive Analyses.

Table 1 displays the baseline descriptive characteristics for the total sample, partitioned by treatment group and race-ethnicity. The mean (SD) age of the overall sample was 66.8 (9.7) years. Collectively, referring to Table 1, columns “T” to “K”, some significant differences between the treatments within racial/ethnic subgroups were observed. Among NHWs, (column “T”), participants in the intensive treatment group had significantly lower mean serum glucose concentrations compared to those in the standard treatment group. Among NHB participants (column “J”), participants in the intensive treatment group reported significantly lower baseline IIEF-5 scores, and were more likely to be ≥ 75 years of age and to have been prescribed cholesterol lowering medications, and had higher mean serum glucose concentrations and PHQ-9 scores compared to participants in the standard treatment group. Among Hispanic and other races (H/O) participants, those in the intensive treatment group reported higher weekly alcohol use compared to participants in the standard treatment group.

Figures 1 and 2 (Panels A, B and C) display the mean (SD) achieved systolic and diastolic blood pressures for the two treatments in the HRQL subsample according to race-ethnicity. As observed in previous SPRINT analyses (10;18), the smaller sample sizes and larger variability for the later visits reflect the early termination of the trial. At the 48-month visit, for all participants in the intensive treatment group, the mean SBP (SD) was 120.1 (2.2) mm Hg, and 135.5 (1.0) for participants in the standard treatment group. Figure 2 displays the mean (SD) achieved diastolic blood pressures (DBPs) for the two treatments and three racial/ethnic groups. At the 48-month visit, the mean DBP for participants in the intensive treatment group was 65.7 (1.1) mm Hg, and 76.3 (1.3) mm Hg for participants in the standard treatment group. For NHW and H/O, the mean number of medications in the standard group remained relatively unchanged over time, while the mean number of medications among NHBs in the standard group appeared to have increased slightly over the course of the study. In all race/ethnicity groups, the mean number of medications in the intensive treatment group increased slightly over time.

Mixed Linear Model Analyses.

As noted earlier, the linear mixed model found a significant treatment group by race-ethnicity interaction ($p = 0.0016$). Figure 3 (Panels A, B, and C) presents the sample sizes, estimated least square means, and 95% confidence intervals for the mixed linear models conducted to assess the effect of the two treatments on change in IIEF-5 total scores from baseline for each race-ethnicity subgroup. In **Panel A** (NHWs), participants in the intensive treatment group reported more favorable change in erectile function compared to participants in the standard treatment group, with a mean difference in change (95% CI) of +0.67 (0.03, 1.32) points; $p = 0.041$. If the model is adjusted for baseline IIEF-5 score, the

effect becomes non-significant, $p=0.060$, with an estimated difference of $+0.57$ (-0.03 , 1.17). In NHB participants (**Panel B**), participants in the intensive treatment group reported less favorable change in erectile function compared to participants in the standard treatment group, with a mean difference of change (95% CI) of -1.17 points (-1.92 , -0.41); $p=0.0025$. *However, once baseline IIEF score is added to the model, the effect is no longer significant ($p=0.12$), with a mean estimated difference of -0.54 , 95% CI of (-1.23 , 0.15).* Among H/O participants (**Panel C**), there was no significant difference in change in IIEF-5 scores according to treatment group, with intensive group participants reporting a mean difference of change (95% CI) of $+0.60$ (-0.80 , 1.99) units; $p=0.40$ compared to participants in the standard treatment group. In NHB participants (**Panel B**), a significant treatment by visit interaction was observed ($p=0.018$). However, as the sample size at year 4 was very small ($n=45$), this result may have been due to random fluctuation in scores; thus no further follow-up analyses were performed.

Cox Proportional Hazard Model Analyses.

Table 2 depicts the results of the Cox models conducted to compare ED incidence in the two treatment arms among participants whose IIEF-5 scores were >21 (no ED) at baseline. Event rates for the two treatments were similar over the duration of the study, with a cumulative incidence rate of 71.6% in the standard treatment group vs. 64.6% in the intensive treatment group. The rates of the two treatments of incident ED were similar (hazard ratio for intensive treatment vs. standard treatment 1.11; 95% CI 0.80, 1.54; $p=0.53$).

DISCUSSION

The primary purpose of this investigation was to assess whether hypertensive men in SPRINT who were randomly assigned to either standard or more intensive blood pressure control treatment differed in their self-reported change in erectile function from baseline in longitudinal analyses, and to consider whether race-ethnicity moderated this effect. In addition, in a subgroup of participants who did not report ED at baseline, we assessed whether the incidence of self-reported ED differed in the standard and intensive treatment groups. Collectively, we observed that the effect of the intensive intervention upon change in erectile function differed according to race-ethnicity, with NHW participants in the intensive treatment group reporting significantly better change in erectile function, while NHB participants in the intensive treatment group reported significantly worse change in erectile function. However, the magnitude of difference in IIEF-5 scores for each racial-ethnic group was very small. In addition, the two treatment groups did not differ in incidence of ED. These findings provide important evidence that, along with reducing the risk of cardiovascular disease and mortality, intensive blood pressure control does not result in unduly unfavorable impact upon erectile function compared to standard treatment.

Baseline descriptive analyses of the overall sample found that the mean score of the IIEF-5 (Table 1) was 18.0, suggestive of mild ED (score of 17 to 21) (20). Nearly two-thirds (66.1%) had IIEF-5 scores suggestive of ED (score ≥ 21), which is consistent with other reports of middle aged and older men with hypertension (often with diabetes) (25;26). We also observed that 10.5% of the total sample were taking PDE-5 inhibitors, which have been

shown to be safe and effective in improving erectile function (27), although it must be noted that PDE-5 inhibitors are used for treatment of other cardiac, circulatory, and neurogenerative conditions (28). Despite the high prevalence of ED by self-report, we found that more than two-thirds (68.3%) of participants reported engaging in sexual activity over the past 4 weeks at baseline. Taken as a whole, these findings suggest that many men with hypertension are sexually active, even though many of them may have ED. Indeed, as ED is increasingly being acknowledged as not only as a consequence, but a possible harbinger of vascular disease (29;30), and men with ED may not seek medical advice, clinicians can play a useful role by routinely assessing erectile function in men with hypertension, which may facilitate referral to specialists.

Interestingly, the linear mixed model detected that the effect of intensive treatment for blood pressure upon erectile function was significantly moderated by race-ethnicity. To our knowledge, this is the first observation of this association, and there are several plausible baseline factors that may have contributed to this finding. Of importance, SPRINT did not include eligibility criteria regarding sexual function; thus, it is not surprising that there were differences at baseline in several variables related to erectile function in the racial-ethnic groups. As noted earlier, some classes of antihypertensive medications, such as thiazide and thiazide-type diuretics, have been associated with ED, and at baseline, a higher percentage of NHB participants in the intensive blood pressure lowering group were taking diuretics compared to NHW and H/O participants, although it must be noted that the literature regarding the role of antihypertensive agents in contributing to ED is discordant (31;32). Also, blood glucose levels and depressive symptoms (33) have each been associated with erectile function, and NHB participants in the intensive blood pressure lowering group had higher baseline levels of blood glucose and PHQ-9 scores than other treatment-race/ethnicity subgroups. In addition, NHB participants in the standard treatment reported the highest mean baseline IIEF-5 scores among the treatment/racial-ethnic subgroups, while NHB participants in the intensive treatment group reported the highest percentage of ED and of use of PDE-5 inhibitors among the treatment/racial-ethnic groups. Interestingly, however, NHB participants reported higher percentages of being sexually active the past 4 weeks compared to the other treatment/racial-ethnic subgroups. Collectively, these baseline characteristics present a complex conglomeration of factors that may have influenced the trajectory of IIEF-5 scores independent of intensive blood pressure control.

We had acknowledged that more intensive treatment of hypertension may result in less favorable erectile function, and a possible explanation for this result may reside in the effect of the intensive intervention upon SBP and DBP. Achieved SBPs were 8.3 mmHg lower in NHBs compared with NHWs at the 48-month visit. Lower achieved SBPs could have reduced perfusion to penile tissue, and might have contributed to the differential trend in self-reported erectile function among NHB and NHW participants. In a previous SPRINT investigation, we observed in cross-sectional analyses of baseline data using multivariable linear regression that DBP was directly correlated with erectile function (i.e, higher DBP was associated with better erectile function), possibly related to the link between arteriosclerosis and vascular stiffness and lower DBP and wider pulse pressures (21). Similar results were observed in separate cross-sectional analyses by Korhonen et al. (34) and Heikkilä et al. (35) who each found a U-shaped association between DBP and prevalence of

ED, with an optimal nadir occurring at 90 mm Hg. Referral to Figure 2 (Achieved DBPs) indicates that at 48 months, the mean DBP in NHBs in the intensive intervention group was 67.7 mm Hg. As erectile function involves complex hemodynamic, neuronal and vascular processes of vasodilation and vasoconstriction, a threshold SBP and DBP may be necessary to maintain sufficient perfusion to enable erection or coitus (35).

However, it must be noted that although the differences in trajectory of change in self-reported erectile function by race/ethnicity were statistically significant, the observed difference in change in estimated means from baseline was small. In addition, the changes in IIEF-5 scores over time were stable for racial-ethnic groups in the two treatments. For example, in NHW and H/O participants, the mean difference in change in IIEF-5 scores in the two treatments was < 1 point, and for NHB participants the difference in change in scores was 1.17 points. Indeed, addition of baseline IIEF-5 score to the model resulted in complete attenuation of the effect of treatment group upon change in IIEF-5 score. These findings raise the question of whether these small changes in scores were clinically significant. Rosen et al., developers of the original 15-item IIEF (36) and the IIEF-5 (20) have stated that patients who reported mild ED from the 6-item erectile function domain of the original IIEF would need to report a 2-point difference to meet or exceed a minimal clinically-significant difference (MCID) (37). If this criterion were applied, the differences in scores would not be deemed as clinically significant. However, to our knowledge, MCIDs for the IIEF-5 have not been established, and Chew (38) has warned that the application of MCIDs from one instrument to another may lead to different conclusions.

This study has several strengths, including use of data from a randomized trial, direct and rigorous assessment of blood pressure, clinical measures, anthropometric measures and antihypertensive medications in a large, multiethnic sample. In addition, this study included a validated measure of self-reported sexual function, and had a large percentage of participants (68.3%) who reported being sexually active at baseline. However, this study has several limitations. As noted by the developers of the IIEF-5, this instrument focuses on erectile function and does not assess multiple dimensions of sexual function. In addition, the IIEF-5 assesses erectile function over the preceding 4 weeks, which would deem a person who had engaged in sexual activity over the past 5 weeks as sexually inactive. In addition, we did not ask participants why they had not engaged in sexual activity and we did not assess chronicity of hypertension or ED. Also, due to the possibly sensitive nature of questions in the IIEF-5, some participants may have chosen to provide socially desirable responses regarding sexual activity and erectile function. SPRINT only enrolled participants with hypertension, which prevented comparisons of erectile function in men with hypertension vs. without hypertension, and did not enroll individuals with diabetes. SPRINT also did not initially assess relationship status (e.g., marital or partnered status), and did not assess quality of relationships. Also, we did not assess zinc, testosterone or androgen levels, or hydration or volume status; nor did we assess changes in class of antihypertensive medication or PDE-5 inhibitor use in this investigation. In addition, this sample was highly educated, with 75.9% of participants reporting post-high school education. While this is not a disadvantage (and may improve the reliability of questionnaires), it may limit the generalizability of our findings.

In this investigation of middle-aged and older men with hypertension, we found that more intensive SBP lowering did not materially influence self-reported erectile function and did not influence the incidence of erectile dysfunction in participants with normal or near normal erectile function at baseline. Moreover, while the trajectory in self-reported erectile function differed significantly according to race-ethnicity, the small differences were unlikely to be clinically relevant in the vast majority of participants. In addition, rates of incident ED were similar in the two treatment groups, and were not moderated by race-ethnicity. In the context of the primary results from SPRINT indicating that intensive control results in beneficial cardiovascular outcomes (10), and previous SPRINT findings regarding patient-reported outcomes (12), these results suggest that intensive control of BP does not result in deleterious effects on erectile function, although further study of the association of moderating effect of race/ethnicity is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

FUNDING AND ACKNOWLEDGEMENTS

The manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language. The Systolic Blood Pressure Intervention Trial is funded with Federal funds from the National Institutes of Health (NIH), including the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Aging (NIA), and the National Institute of Neurological Disorders and Stroke (NINDS), under Contract Numbers HHSN268200900040C, HHSN268200900046C, HHSN268200900047C, HHSN-268200900048C, HHSN268200900049C, and Inter-Agency Agreement Number A-HL-13-002-001. It was also supported in part with resources and use of facilities through the Department of Veterans Affairs. The SPRINT investigators acknowledge the contribution of study medications (azilsartan and azilsartan combined with chlorthalidone) from Takeda Pharmaceuticals International, Inc. All components of the SPRINT study protocol were designed and implemented by the investigators. The investigative team collected, analyzed, and interpreted the data. All aspects of manuscript writing and revision were carried out by the co-authors. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, the U.S. Department of Veterans Affairs, or the United States Government. For a full list of contributors to SPRINT, please see the supplementary acknowledgement list, <http://links.lww.com/HJH/A879>:

ClinicalTrials.gov Identifier: NCT01206062. We also acknowledge the support from the following CTSA's funded by NCATS: CWRU: UL1TR000439; OSU: UL1RR025755; U Penn: UL1RR024134 and UL1TR000003; Boston: UL1RR025771; Stanford: UL1TR000093; Tufts: UL1RR025752; UL1TR000073 and UL1TR001064; University of Illinois: UL1TR000050; University of Pittsburgh: UL1TR000005; UT Southwestern: 9U54TR000017-06; University of Utah: UL1TR000105-05; Vanderbilt University: UL1TR000445; George Washington University: UL1TR000075; University of California, Davis: UL1TR000002; University of Florida: UL1TR000064; University of Michigan: UL1TR000433; Tulane University: P30GM103337 COBRE Award NIGMS. Sources of funding support: The sources of support information for this analysis are listed above. For a full list of contributors to SPRINT, please see the supplementary acknowledgement list: ClinicalTrials.gov Identifier: NCT01206062

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Figure 1.
Mean Systolic Blood Pressures, and Number of Antihypertensive Medications According to Race/Ethnicity and Treatment Group

In Panels A, B, and C, the mean number of medications is the number of blood pressure medications administered at the exit of each visit. The bars represent 95% confidence intervals. Please note that the vertical axis for Panel C has a slightly different range compared to Panels A and B.

Figure 2.

Mean Diastolic Blood Pressures, and Number of Antihypertensive Medications According to Race/Ethnicity and Treatment Group

In Panels A, B, and C, the mean number of medications is the number of blood pressure medications administered at the exit of each visit. The vertical bars represent 95% confidence intervals. Please note that the vertical axis for Panel C has a slightly different range compared to Panels A and B.

Figure 3.

Change in International Index of Erectile Function (IIEF-5) Scores over the Course of the Study, by Racial/Ethnic and Treatment Group

For Panels A, B and C, the data points represent the estimated mean change in scores from baseline in the two treatment groups over time. The mean number of medications is the number of blood pressure medications administered at the exit of each visit. The vertical bars represent 95% confidence intervals. Scores on the IIEF-5 range from 5 to 25, with lower scores suggesting poorer erectile function.

Table 1.
Baseline Characteristics of SPRINT Participants, Stratified by Race-Ethnicity and Treatment Group

Characteristic	A: Overall Total Sample N = 1290	Non-Hispanic White (NHW) (N = 770)		Non-Hispanic Black (NHB) (N = 358)		Hispanic or Other (H) (N = 162)		H: p-value for Race Treatment Subgroup (B,C,D,E,F,G)	I: p value for Intensive vs. Standard Treatment NHW (B, C)	J: p value for Intensive vs. Standard Treatment NHB (D, E)	K: p value for Intensive vs. Standard Treatment H (F, G)
		B: Intensive (n = 383)	C: Standard (n = 387)	D: Intensive (n = 171)	E: Standard (n = 187)	F: Intensive (n = 78)	G: Standard (n = 84)				
Sexually Active within past 4 weeks ^b	857 (68.3)	241 (64.6)	250 (66.7)	135 (79.9)	129 (72.5)	51 (66.2)	51 (61.5)	0.0052	0.55	0.11	0.53
International Index of Erectile Function (IIEF-5) ^a	18.0 (5.8)	17.5 (6.1)	17.5 (6.4)	17.7 (5.5)	19.4 (4.4)	18.6 (5.8)	18.7 (5.3)	0.036	0.95	0.0062	0.93
Erectile Dysfunction ^{b, f}	545 (66.1)	156 (67.8)	154 (63.6)	93 (71.0)	80 (65.0)	31 (62.0)	31 (63.3)	0.70	0.34	0.31	0.90
<i>Demographic</i>											
Age (yrs.) ^a	66.8 (9.7)	69.8 (8.7)	69.1 (9.4)	61.9 (9.4)	63.2 (9.0)	62.3 (8.0)	65.4 (10.7)	0.0001	0.34	0.039	0.17
Age 75 yrs. ^b	336 (26.1)	133 (34.7)	127 (32.8)	25 (14.6)	26 (13.9)	5 (6.4)	20 (23.8)	<0.0001	0.57	0.0022	0.85
<i>Race/Ethnicity^b</i>											
Non-Hispanic White ^b	770 (59.7)										
African-American ^b	358 (27.8)										
Hispanic ^b	140 (10.8)										
Other ^b	22 (1.7)										
<i>Education^b</i>											
Less than High School ^b	107 (8.3)	21 (5.5)	12 (3.1)	23 (13.5)	25 (13.4)	10 (12.8)	16 (19.0)	<0.0001	0.39	0.25	0.038
High School Graduate/GED ^b	204 (15.8)	52 (13.6)	49 (12.7)	38 (22.2)	47 (25.1)	4 (5.1)	14 (16.7)				
Post High School ^b	460 (35.7)	130 (33.9)	133 (34.4)	81 (47.4)	71 (38.0)	22 (28.2)	23 (27.4)				

Characteristic	A: Overall Total Sample N = 1290	Non-Hispanic White (NHW) (N = 770)		Non-Hispanic Black (NHB) (N = 358)		Hispanic or Other (H) (N = 162)		H: p-value for Race Treatment Subgroup (B,C,D,E,F,G)	I: p value for Intensive vs. Standard Treatment NHW (B, C)	J: p value for Intensive vs. Standard Treatment NHB (D, E)	K: p value for Intensive vs. Standard Treatment H (F, G)
		B: Intensive (n = 383)	C: Standard (n = 387)	D: Intensive (n = 171)	E: Standard (n = 187)	F: Intensive (n = 78)	G: Standard (n = 84)				
College Degree ^b	519 (40.2)	180 (47.0)	193 (49.9)	29 (17.0)	44 (23.5)	42 (53.9)	31 (36.9)				
Lives with Others ^b	980 (76.0)	297 (77.6)	295 (76.2)	123 (72.4)	131 (70.1)	62 (79.5)	72 (85.7)	0.068	0.66	0.63	0.29
Behavioral Risk Factors											
Smoking (pack-yrs.) [§]	14.9 (23.0)	18.5 (25.2)	17.3 (25.4)	9.9 (14.6)	11.0 (20.0)	10.8 (17.9)	9.9 (20.9)	<0.0001	0.49	0.56	0.77
Alcohol (drinks/typical week) [§]	1.4 (1.6)	1.3 (1.6)	1.4 (1.3)	1.3 (1.7)	1.4 (1.5)	2.2 (2.4)	1.5 (1.9)	0.0007	0.51	0.56	0.039
Antihypertensive Medication Use											
Use of Beta-Blockers ^b	403 (31.2)	139 (36.3)	147 (38.0)	43 (25.2)	36 (19.3)	22 (28.2)	16 (19.0)	<0.0001	0.63	0.18	0.17
Use of Diuretics ^b	545 (42.2)	147 (38.4)	152 (39.3)	93 (54.4)	98 (52.4)	22 (28.2)	33 (39.3)	<0.0001	0.80	0.71	0.14
Use of Calcium Channel Blockers ^b	451 (35.0)	115 (30.0)	120 (31.0)	76 (44.4)	82 (43.9)	27 (34.6)	31 (36.9)	0.0012	0.77	0.91	0.76
Use of Angiotensin Converting Enzyme Inhibitors ^b	521 (40.4)	156 (40.7)	159 (41.1)	69 (40.4)	75 (40.1)	32 (41.0)	30 (35.7)	0.97	0.92	0.96	0.49
Use of Angiotensin Receptor Blockers ^b	220 (17.1)	68 (17.7)	70 (18.1)	21 (12.3)	20 (10.7)	17 (21.8)	24 (28.6)	0.0034	0.90	0.64	0.32
Total Number of Antihypertensive Medications ^a	1.8 (1.0)	1.8 (1.0)	1.8 (1.0)	2.0 (1.1)	1.8 (1.0)	1.7 (1.0)	1.7 (0.9)	0.16	0.84	0.15	0.93
Cardiometabolic and Psychosocial Variables											
Glucose (mg/dL) ^a	99.5 (12.5)	99.0 (12.1)	100.9 (11.3)	101.1 (15.8)	96.4 (12.3)	100.8 (11.7)	97.1 (11.7)	0.0003	0.029	0.0022	0.046

Characteristic	A: Overall Total Sample N = 1290	Non-Hispanic White (NHW) (N = 770)		Non-Hispanic Black (NHB) (N = 358)		Hispanic or Other (H) (N = 162)		H: p-value for Race Treatment Subgroup (B,C,D,E,F,G)	I: p value for Intensive vs. Standard Treatment NHW (B, C)	J: p value for Intensive vs. Standard Treatment NHB (D, E)	K: p value for Intensive vs. Standard Treatment H (F, G)
		B: Intensive (n = 383)	C: Standard (n = 387)	D: Intensive (n = 171)	E: Standard (n = 187)	F: Intensive (n = 78)	G: Standard (n = 84)				
Diabetes ^b	23 (1.8)	5 (1.3)	8 (2.1)	3 (1.8)	5 (2.7)	1 (1.3)	1 (1.2)	0.88	0.58	0.73	>0.99
Systolic Blood Pressure											
(mmHg) ^a	139.0 (14.8)	139.4 (14.2)	139.6 (15.3)	137.5 (16.3)	139.6 (13.8)	138.6 (13.4)	136.9 (14.9)	0.45	0.90	0.19	0.46
Diastolic Blood Pressure											
(mmHg) ^a	78.8 (11.8)	77.4 (10.8)	76.8 (11.6)	82.0 (12.2)	83.3 (12.3)	80.3 (11.5)	76.3 (11.5)	<0.0001	0.51	0.34	0.026
Pulse Pressure											
(mmHg) ^{a, c}	60.2 (13.5)	62.0 (13.1)	62.7 (14.3)	55.4 (12.5)	56.3 (11.8)	58.2 (13.3)	60.6 (13.2)	<0.0001	0.50	0.51	0.25
Total Cholesterol											
(mg/dL) ^a	182.5 (40.4)	178.9 (38.3)	178.7 (40.3)	188.4 (46.2)	188.5 (40.3)	190.8 (36.9)	183.7 (37.1)	0.0035	0.95	0.99	0.22
Any Anti-Cholesterol Medication ^b	696 (53.9)	238 (62.1)	238 (61.5)	74 (43.3)	60 (32.1)	38 (48.7)	47 (57.1)	<0.0001	0.85	0.029	0.28
Any Antidepressant Medication ^b	147 (11.4)	43 (11.3)	45 (11.6)	21 (12.3)	19 (10.2)	8 (10.3)	11 (13.1)	0.98	0.85	0.52	0.57
Phosphodiesterase Type 5 Inhibitors ^b	136 (10.5)	38 (9.9)	30 (7.8)	32 (18.7)	30 (16.0)	3 (3.9)	3 (3.6)	<0.0001	0.29	0.50	>0.99
BMI (kg/m ²) ^a	29.9 (5.4)	29.9 (5.4)	30.0 (5.2)	30.4 (5.3)	29.9 (5.6)	30.2 (6.6)	28.5 (5.3)	0.22	0.73	0.47	0.080
Cardiovascular Disease ^b	304 (23.6)	117 (30.6)	107 (27.7)	28 (16.4)	20 (10.7)	20 (25.6)	12 (14.3)	<0.0001	0.38	0.12	0.078
CVD Family History ^b	286 (24.8)	85 (24.6)	101 (27.9)	33 (23.4)	33 (21.2)	13 (18.3)	21 (26.9)	0.42	0.31	0.64	0.21
Framingham 10-year CVD risk score ^a	29.3 (12.8)	31.1 (12.5)	30.7 (12.5)	25.3 (12.2)	27.8 (13.2)	28.3 (12.6)	27.6 (13.8)	<0.0001	0.67	0.067	0.75

Characteristic	A: Overall Total Sample N = 1290	Non-Hispanic White (NHW) (N = 770)		Non-Hispanic Black (NHB) (N = 358)		Hispanic or Other (H) (N = 162)		H: p-value for Race Treatment Subgroup (B,C,D,E,F,G)	I: p value for Intensive vs. Standard Treatment NHW (B, C)	J: p value for Intensive vs. Standard Treatment NHB (D, E)	K: p value for Intensive vs. Standard Treatment H (F, G)
		B: Intensive (n = 383)	C: Standard (n = 387)	D: Intensive (n = 171)	E: Standard (n = 187)	F: Intensive (n = 78)	G: Standard (n = 84)				
eGFR (mL/min/1.73 m ²) ^a	74.0 (20.6)	70.1 (17.8)	69.9 (17.8)	79.3 (22.4)	80.0 (21.3)	82.8 (25.7)	79.2 (24.7)	<0.0001	0.84	0.78	0.37
^a Chronic Kidney Disease											
(eGFR <60 mL/min/1.73m ²)	318 (24.7)	114 (29.8)	118 (30.6)	27 (15.8)	29 (15.5)	13 (16.7)	17 (20.7)	<0.0001	0.83	0.94	0.51
MoCA Total Score ^{a, d}	23.1 (3.6)	24.0 (3.4)	24.0 (3.1)	21.7 (3.6)	21.3 (3.5)	22.2 (4.0)	21.7 (4.0)	<0.0001	0.95	0.32	0.39
PHQ-9 Total Score ^{g, e}	3.0 (4.2)	2.6 (3.5)	2.9 (3.8)	4.0 (5.4)	3.0 (4.4)	3.1 (4.2)	3.6 (5.4)	0.0065	0.19	0.052	0.55
Number of Physical											
Comorbidities ^{a, e}	4.4 (2.7)	4.9 (2.8)	5.0 (2.9)	3.6 (2.3)	3.2 (2.2)	3.7 (2.4)	3.8 (2.7)	<0.0001	0.80	0.087	0.87
Number of Mental											
Comorbidities ^{a, e}	0.41 (0.88)	0.32 (0.73)	0.36 (0.77)	0.56 (1.04)	0.46 (1.03)	0.49 (0.96)	0.60 (1.13)	0.011	0.48	0.36	0.52

^aData presented as mean (standard deviation)^bData presented as percentage^cDefined as (systolic blood pressure in mmHg – diastolic blood pressure in mmHg)^dHigher scores indicate better function^gData presented as median (25th percentile, 75th percentile)^eHigher scores indicate poorer function^fDefined as IIEF-5 total score 21^{*} p-value from Chi Square test for categorical variables and Student's t-test for continuous variables

Table 2.
Event-free Rates of Erectile Dysfunction* in the Standard and Intensive Treatment Groups over Time

Time (months)	Standard Treatment (n = 131)		Intensive Treatment (n = 149)	
	Event-free % (% reporting ED)	N remaining	Event-free % (% reporting ED)	N remaining
12	66.3 (4.3)	73	63.4 (4.1)	81
24	55.4 (4.6)	52	55.6 (4.2)	60
36	42.6 (4.8)	12	49.1 (4.4)	18
48	28.4 (6.6)	0	35.4 (6.1)	0

* Erectile Dysfunction defined as 5-item International Index of Erectile Function total score ≥ 21