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Published in:
European Heart Journal - Cardiovascular Pharmacotherapy

DOI (link to publication from Publisher):
10.1093/ehjcvp/pvaa102

Publication date:
2021

Document Version
Accepted author manuscript, peer reviewed version

Intensive blood pressure control appears to be effective and safe in patients with peripheral artery disease: The Systolic Blood Pressure Intervention Trial (SPRINT)

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Trial Registration:

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

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Article Type:

Correspondence/Letter

Word Count (≤1000):

1109*

Tables (≤1):

0

Figures (≤1):

1

Abstract:

Not required.

Key Words:

Blood Pressure; Cardiovascular Diseases; Hypertension; Peripheral Arterial Disease; Safety; Vascular Diseases

High blood pressure (BP) is the strongest modifiable risk factor for cardiovascular disease and is highly prevalent among individuals with peripheral artery disease (PAD) (1-3). While patients with atherosclerotic cardiovascular conditions experience considerable morbidity and mortality, the risk is particularly high among those with PAD (4). However, data regarding the effects of strict BP-goals in the setting of PAD are lacking. We leveraged data from the randomized, controlled, open-label Systolic Blood Pressure Intervention Trial (SPRINT) to assess whether the benefits and potential risks of intensive BP-control extended to patients with PAD, and whether baseline PAD modified treatment effect (5).

The full SPRINT clinical data set was acquired from the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordination Center. A waiver for secondary data use was granted by the Brigham and Women's Hospital Institutional Review Board. In SPRINT, 9,361 high-risk individuals without diabetes or prior stroke, aged ≥50 years, with a systolic BP 130-180 mmHg were randomized to intensive (systolic BP target <120mmHg; n=4678) or standard BP-control (systolic BP target 135-139 mmHg; n=4683) (5). The primary outcome was the composite of acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes. We used Cox proportional-hazards regression to determine the efficacy and safety of intensive versus standard BP-control in patients with and without self-reported lower extremity PAD at baseline. Subgroup heterogeneity was examined using the likelihood-ratio test.

Of 9361 participants, 503 (5.3%) had baseline PAD (intensive group 250 (5.3%) versus standard group 253 (5.4%); P=0.90). The presence of PAD was associated with male sex (P<0.001), older age (P<0.001), current or former smoking (P<0.001), use of more antihypertensives (P<0.001), lower total cholesterol (P<0.001), lower high-density lipoprotein cholesterol (P=0.005), higher serum creatinine (P<0.001), and higher urine albumin-to-creatinine ratio (P<0.001). Median follow-up durations were 3.2 years (range 0-4.6 years) and 3.3 years (range 0-4.8 years) for patients with and without PAD, respectively. After adjusting for differences in baseline characteristics, PAD was independently associated with a higher risk of both the primary outcome (hazard ratio 1.61, 95% confidence interval: 1.23-2.12; P<0.001) and composite serious adverse events (hazard ratio 1.49, 95% confidence interval: 1.32-1.69; P<0.001). However, the presence of PAD did not significantly modify the efficacy and safety of intensive versus standard BP-control (P≥0.05) (**Figure 1**). Owing to the higher baseline risk in PAD patients, the absolute risk reductions of the primary outcome, death from cardiovascular causes, and death from any cause appeared larger in participants with PAD. Conversely, relative and absolute increases in the risk of adverse events with intensive BP-control were generally higher in those with PAD (**Figure 1**). In a sensitivity analysis, the effects of intensive BP-control

among patients with prevalent clinical cardiovascular disease largely resembled those found for individuals without a history of cardiovascular disease (**Figure 2**).

Our post hoc analysis of SPRINT showed a higher risk of both efficacy and safety outcomes among patients with PAD. While we did not detect any significant heterogeneity in relative risk differences with intensive versus standard BP-control, patients with PAD seemed to experience numerically greater absolute risk reductions of the efficacy outcomes as well as greater absolute risk increases of the safety outcomes, with intensive treatment. Limitations included the small sample size and lack of patients with diabetes as well as objective measures of PAD.

A theoretical concern in patients with PAD is the exacerbation of limb ischemia with excessive BP-lowering (2,3,6). However, while some studies have suggested an association between low BP and PAD-related events, others have found a reduction in cardiovascular events with antihypertensive treatment (3). Furthermore, in our study, the risk of adverse events with intensive BP-control was relatively higher in the PAD group. Balancing the efficacy and safety of intensive versus standard BP-control in this vulnerable patient population is, therefore, challenging. Nevertheless, the possible mortality benefit with a strict BP-target among patients with PAD is worth noting. Conclusively, we agree with contemporary guideline recommendations that patients with hypertension and PAD should be treated in a similar fashion to patients with hypertension without PAD (1).

Acknowledgements

None.

Funding

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 Honorarium: AstraZeneca; Bayer; Boehringer Ingelheim.

Dr. Muthiah Vaduganathan is supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst (NIH/NCATS Award UL 1TR002541), serves on advisory boards for Amgen, AstraZeneca, Baxter Healthcare, Bayer AG, and Boehringer Ingelheim, and participates on clinical endpoint committees for studies sponsored by Novartis and the NIH.

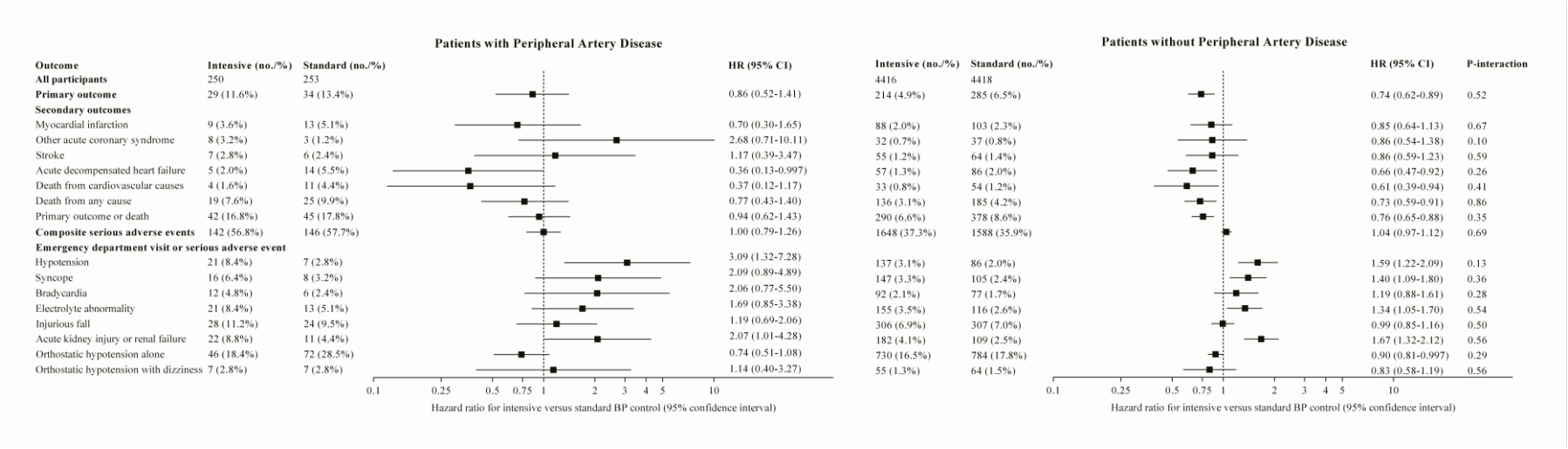
Dr. Tor Biering-Sørensen discloses the following relationships – Steering Committee member of the Amgen financed GALACTIC-HF trial; Advisory Board: Sanofi Pasteur, Amgen; Speaker Honorarium: Novartis, Sanofi Pasteur.

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

Dr. Deepak L. Bhatt discloses the following relationships – Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, PhaseBio, PLx Pharma, 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 (including for the ExCEED trial, funded by Edwards), 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; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, 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, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, 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, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda.

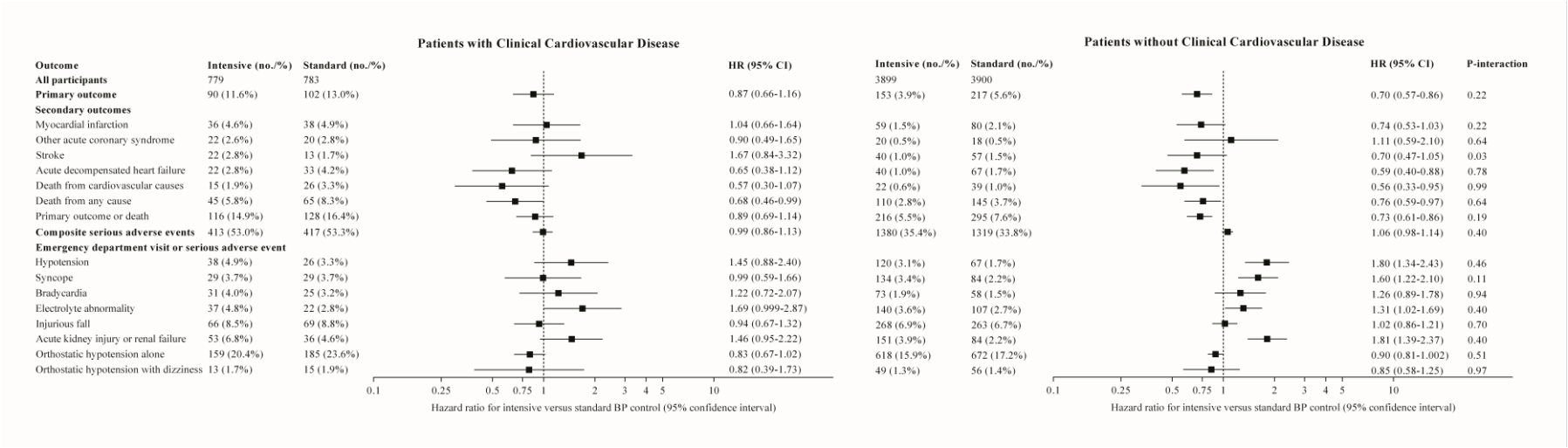
The other authors report no relevant disclosures.

Figure 1. Efficacy and safety events with intensive versus standard blood pressure control in patients with and without peripheral artery disease.



Abbreviations: CI = confidence interval; HR = hazard ratio.

Figure 2. Efficacy and safety events with intensive versus standard blood pressure control in patients with and without clinical cardiovascular disease.



Abbreviations: CI = confidence interval; HR = hazard ratio.

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Figure 1

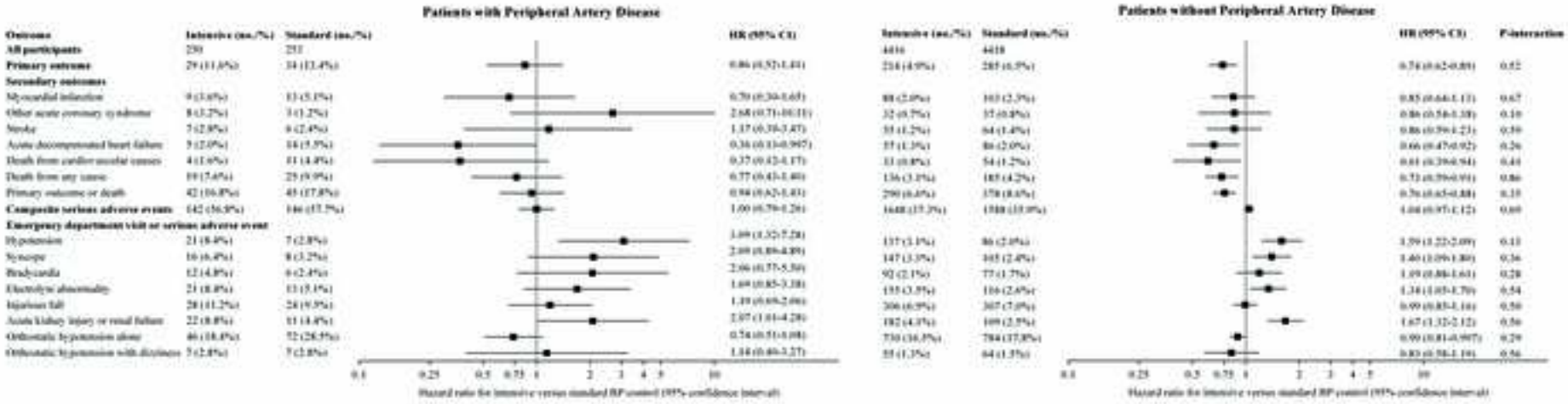

Figure 2