www.cpha.com
California Pharmacist 2017
A peer-reviewed publication of the California Pharmacists Association

EVIDENCE BASED PRACTICE

# SPRINT Trial

By Dana Hassid, PharmD candidate; David Lash, PharmD, MPH; Cynthia A. Jackevicius, BScPhm, PharmD, MSc, BCPS-AQ Cardiology, FCSHP, FAHA, FCCP, FCCS

## ARTICLE HISTORY
Published: April 2017

## SPRINT TRIAL OVERVIEW
**Patient Population:** age at least 50 years old, systolic blood pressure (SBP) 130 to 180 mmHg and at an increased risk of cardiovascular events. Patients with diabetes mellitus or prior stroke were excluded.
**Intervention:** intensive blood pressure treatment (INT) with SBP goal of <120 mmHg.
**Comparison:** standard blood pressure control (STD) with SBP goal of <140 mmHg.
**Outcome:** cardiovascular (CV) events; myocardial infarction (MI), acute coronary syndromes (ACS), stroke, heart failure or death from cardiovascular causes.
**Time Frame:** the intervention was stopped early after a median follow-up of 3.26 years.

## I. Trial Validity

| | Risk of Bias | | |
|---|---|---|---|
| **Start of Trial** | **High** | **Possible/ Unclear** | **Low** |
| **Randomization/Concealment** | | | |
| • Patients were randomized to standard SBP control (target <140 mmHg) or intensive SBP control (target <120 mmHg) using a computerized, web-based system.<br>• Centralized randomization through a web-based system maintained concealment of treatment allocation. | | | X |
| **Baseline Characteristics** | | | |
| • Baseline characteristics were similar between the two groups except in statin use (44.7% in STD versus 42.6% in INT) and aspirin use (50.4% in STD versus 51.6% in INT). Both aspirin and statins reduce the risk for the composite primary endpoint of CV outcomes. However, because statin use is higher in the STD group, while aspirin use is higher in the INT group, the overall direction of bias is unclear. Otherwise, the groups were well-balanced. | | X | |

 

| | Risk of Bias | | |
|---|---|---|---|
| **During Trial** | **High** | **Possible/ Unclear** | **Low** |
| **Blinding** | | | |
| SPRINT was not blinded for patients or study personnel, but the clinical outcomes adjudication committee was blinded.<br>☒ Patient - No blinding in this study<br>☒ Clinician/investigator - No blinding in this study<br>☑ Outcomes/endpoints assessors - Blinded in this study<br>☐ Data collectors - No information about blinding<br>☐ Data analysts - No information about blinding<br>Unblinded patients and clinician/investigator may bias the results in favor of the treatment group. | X | | |
| **Equal Treatment** | | | |
| • Because patients and clinicians were not blinded, the possibility of contamination and co-intervention exists.<br>• Contamination, which would occur if the STD group received the same therapy as the INT group, is unlikely. The SBP differences between groups suggest that contamination did not occur. All major classes of antihypertensive agents were included in the formulary and were provided at no cost. Table S2 indicates that the intensive treatment group was treated with an average of 2.7 antihypertensive medications, and the standard treatment group, an average of 1.8 medications, confirming the expected gap in intensity of therapy, which argues against contamination.<br>• Co-interventions are other interventions aside from the strategy of blood pressure intensity that may influence the occurrence of the outcome. Lifestyle modification was encouraged in SPRINT, but the study did not provide further information on co-interventions that would affect CV morbidity and mortality such as diet, exercise, and over-the-counter medication use. The baseline differences in aspirin (ASA) and statin use are co-interventions that improve CV outcomes. However, the direction of the overall bias is unclear. | | X | |
| **End of Trial** | **High** | **Possible/ Unclear** | **Low** |
| **Completeness of Outcome Data** | | | |
| • SPRINT was stopped early after a median 3.26 years of follow-up due to a significantly lower rate of the primary composite outcome in the INT group.<br>• A total of 255 out of 4,683 patients (5.4%) in the STD group and 265 out of 4,678 patients (5.7%) in the INT group had missing outcomes data. Both treatment groups had a similar percentage of patients who did not have final outcomes measured.<br>• However, the percentage of patients with missing outcomes data (5.6%) is of greater magnitude than the absolute risk reduction of composite CV outcomes between groups (1.6%), which may bias the results in favor of the INT treatment group. | X | | |
| **Method of Outcome Analysis** | | | |
| • The authors used intention-to-treat for all statistical analyses. | | | X |

 

## II. Trial Results

| Efficacy Outcome | Standard Treatment N= 4,683 | Intensive Treatment N= 4,678 | Hazard Ratio (HR) and 95% Confidence Interval (CI) | Relative Risk Reduction (RRR) | Absolute Risk Reduction (ARR) | Number Needed to Treat (NNT) | P-value |
|---|---|---|---|---|---|---|---|
| Primary Endpoint Composite[1] | 319 (6.8%) | 243 (5.2%) | 0.75 (0.64-0.89) | 23.5% | 1.6% | 62 | <0.001 |
| Selected Secondary Endpoints | | | | | | | |
| Myocardial Infarction (MI) | 116 (2.5%) | 97 (2.1%) | 0.83 (0.64-1.09) | 16.0% | 0.4% | - | 0.19 |
| Stroke | 70 (1.5%) | 62 (1.3%) | 0.89 (0.63-1.25) | 13.3% | 0.2% | - | 0.50 |
| Heart Failure | 100 (2.1%) | 62 (1.3%) | 0.62 (0.45-0.84) | 38.1% | 0.8% | 125 | 0.002 |
| Cardiovascular Death | 65 (1.4%) | 37 (0.8%) | 0.57 (0.38-0.85) | 42.9% | 0.6% | 166 | 0.005 |

[1]Composite outcome was the first occurrence of MI, ACS not resulting in MI, stroke, acute decompensated heart failure, or death from cardiovascular causes.

There was a modest, statistically significant decrease in the composite primary endpoint for the intensive treatment group. This result was driven by significant decreases in CV death and heart failure, which were similar in direction and magnitude of effect. Differences in stroke and MI were not statistically significant but were numerically lower in the INT group. Treating to an intensive SBP target of <120 mmHg produced a moderate treatment effect.

| Adverse Event | Standard Treatment N= 4,683 | Intensive Treatment N= 4,678 | Absolute Risk Increase (ARI) | Number Needed to Harm (NNH) | P-value |
|---|---|---|---|---|---|
| Hypotension | 66 (1.4%) | 110 (2.4%) | 1.0% | 100 | 0.001 |
| Syncope | 80 (1.7%) | 107 (2.3%) | 0.6% | 166 | 0.05 |
| AKI or ARF[1] | 117 (2.5%) | 193 (4.1%) | 1.6% | 62 | <0.001 |

[1]Acute kidney injury or acute renal failure

There was a notable significant increase in AKI or ARF in the INT group. There was no difference in progression of renal disease between the treatment groups in those with baseline CKD. However, there was an increase in non-CKD patients experiencing a decrease in eGFR of 30% or more in the intensive treatment group (1.21% per year) compared to standard treatment (0.35% per year). Although those in the INT group did experience more hypotension and syncope, there was no difference in injurious falls (2.2% INT versus 2.3% STD, p=0.71).

## III. Trial Applicability

| | |
|---|---|
| Patient Applicability | • The study results apply to patients 50 years and older, with a SBP of 130 to 180 mmHg who are at an increased risk of cardiovascular events.<br>• Patients with diabetes mellitus or prior stroke were excluded from the study; study results should not be applied to these patients.<br>• On average, patients were 68 years old, obese, Caucasian males with a Framingham 10-year CV risk score of 20%, estimated GFR of 71 ±20 ml/min/1.73 $m^2$, and a baseline SBP of 140 mmHg. |
| Intervention Applicability | • Intensive BP treatment is an accessible and feasible intervention. Attainment of the intensive BP goal required an average of one additional medication compared to standard treatment, which may increase the risk of medication nonadherence.<br>• The standard treatment arm was a reasonable comparison, as patients were treated to the current guideline-based SBP recommendations. |

 

| | |
|---|---|
| Patient-Important Outcomes Measured | • The primary outcome was a composite endpoint of clinical cardiovascular events, including MI, ACS without MI, stroke, heart failure, and death from CV causes. Other clinically relevant endpoints, such as death from any cause, were also evaluated.<br>• Safety endpoints such as AKI and ARF, falls, hypotension, and syncope were all recorded and evaluated.<br>• The primary, secondary, and safety outcomes assessed in SPRINT were all clinically important endpoints. |
| Balance of Benefits vs. Harms | • Treatment to a more intensive SBP goal of <120 mmHg may moderately decrease risk of CV events (p<0.001), but this benefit was associated with increased risk of serious adverse events of AKI or ARF (p<0.001) and hypotension (p=0.001).<br>• Specifically, the study showed that intensive SBP control decreased cases of ADHF (HR 0.62 (0.45-0.84); P=0.002) and cases of CV-related deaths (HR 0.57 (0.38-0.85); P=0.005) but increased cases of AKI or ARF (HR 1.66, 95% CI not given; P<0.001) and hypotension (HR 1.67, 95% CI not given; p<0.001).<br>• If 1,000 hypertensive patients at increased risk of CV events were treated to a SBP goal of <120 mmHg compared to <140 mmHg with a median follow-up of 3.3 years, there would be 16 fewer cases of combined MI, ACS without MI, stroke, heart failure, or CV death. However, there would be an additional 10 cases of hypotension and an additional 16 cases of acute kidney injury or acute renal failure. |

### Health Care Professional Summary

The SPRINT trial was a randomized, concealed, open-label trial with blinded outcomes assessors and ITT analysis. The open-label design, possible co-intervention, and percentage of patients with missing outcomes data (5.6%) greater than the observed absolute risk difference (1.6%) introduce moderate risk of bias into the trial methods. In the SPRINT trial, intensive BP control (SBP <120 mmHg) reduced the absolute risk of composite CV events, including MI, ACS not resulting in MI, stroke, acute decompensated heart failure, or death from cardiovascular causes for those at increased risk of CV events by 1.6% (p<0.001) compared to standard BP control (SBP <140 mmHg), NNT=62.

Patients in the intensive treatment group also experienced an increase in adverse events, including acute kidney injury or acute renal failure (absolute risk increase 1.6%, p<0.001, NNH 62), hypotension (ARI 1.0%, p=0.001, NNH 100), and syncope (ARI 0.6%, p=0.05, NNH 166). Patients 50 years and older with hypertension and an increased risk of CV events were included in the study, while those with diabetes mellitus and those with a history of stroke were excluded from the study.

### Patient Summary

Further decreasing blood pressure led to fewer heart-related events, including death in non-diabetic patients over 50 years old who have high blood pressure but do not have a medical history of stroke. The stricter blood pressure goal caused more kidney damage and more dizziness. Patients needed an average of three medications to get to the stricter goal compared to two medications to get to the less strict goal.

## About the Authors

Dana Hassid, PharmD candidate, is a fourth year student pharmacist at Western University of Health Sciences College of Pharmacy. Ms. Hassid has no conflicts of interest to report.

David Lash, PharmD, MPH, is a pharmacist at Kern Medical Center in Bakersfield, CA. At the time of this manuscript, he was a Cardiovascular Outcomes Research Fellow at Western University of Health Sciences College of Pharmacy under the direction of Dr. Cynthia Jackevicius. Dr. Lash has no conflicts of interest to report.

Cynthia A. Jackevicius, BScPhm, PharmD, MSc, BCPS-AQ Cardiology, FCSHP, FAHA, FCCP, FCCS, is a Professor of Pharmacy Practice at Western University of Health Sciences College of Pharmacy, a Clinical Pharmacy Specialist in Cardiology at VA Greater Los Angeles Healthcare System, a Senior Adjunct Scientist at the Institute for Clinical Evaluative Sciences, and an Associate Professor in the Institute for Health Policy, Management and Evaluation at the University of Toronto. Dr. Jackevicius has no conflicts of interest to report.

## About the Editor

Cynthia Jackevicius, PharmD, a Professor of Pharmacy Practice at Western University of Health Sciences, is the Evidence-Based Practice Section Editor. Dr. Jackevicius teaches evidence-based practice skills to health care professionals. She advocates for the adoption of an evidence-based practice, incorporating the best available evidence, patients' values and preferences, and clinicians' expertise into clinical decision-making.

## Reference

JT Wright, JD Williamson, PK Whelton, et al. A Randomized Trial of Intensive Versus Standard Blood Pressure Control. N Engl J Med 2015; 373:2103-16. DOI: 10.1056/NEJMoa1511939.