Main Outcomes of the Systolic Blood Pressure Intervention Trial (SPRINT) in Patients Age 75 and Older

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Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years: A Randomized Clinical Trial

Published May 19, 2016

Available at jama.com and on The JAMA Network Reader at mobile.jamanetwork.com
Outline

1. Background – How low should we go?
2. SPRINT-Senior
   a) Design and geriatric outcome measures: Frailty status and gait speed
   b) Baseline characteristics
   c) Results by frailty status and gait speed
   d) Adverse events including injurious falls
3. Summary and Conclusions
Prevalence of Hypertension: Age and Sex

- Men
- Women

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American Heart Association
SBP vs stroke mortality risk relationship

- No apparent threshold
- Stroke mortality risk doubles for every 20/10 mm Hg increase above 115/75
- 20 mm Hg increase associated with a 10-fold larger annual absolute stroke risk in 80s vs. 50s.

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Lewington Lancet 2002
Healthy age 60 to 80: What SBP Target?

1. < 120 mm Hg
2. < 140 mm Hg
3. < 150 mm Hg
4. < 160 mm Hg
5. < (100 + age) mm Hg
How low should we go?

- “The panel agreed that more research is needed to identify optimal goals of SBP…” JNC 8
- Equipoise
- Systolic Blood Pressure Intervention Trial (SPRINT) launched in 2010
Background – SPRINT Senior

- Optimal SBP target especially controversial in older, frail patients
  - Epidemiological evidence of inverse relationship between SBP and mortality
  - Concerns regarding falls and fall-related injury due to antihypertensive therapy
  - Cognitive and quality of life outcomes not certain

- ARRA-funded initiative within SPRINT to enhance the number of persons aged 75+ enrolled in the trial

- Ambulatory, community-dwelling older adults

- No nursing home or assisted living facility residents or prevalent dementia enrolled (at baseline)
Major Exclusion Criteria

- Stroke (SPS3)
- Diabetes mellitus (ACCORD)
- Congestive heart failure (symptoms or EF < 35%)
- CKD with eGFR < 20 mL/min/1.73m² (MDRD)
- Standing BP < 110 mm Hg
BP Measurement in SPRINT: Automated Office BP (AOBP)

- Visit BP was the average of 3 seated office BP measurements obtained using an automated measurement device: Omron 907XL.
- Appropriate cuff size was determined by arm circumference.
- Participant was seated with back supported and arm bared and supported at heart level.
- Device was set to delay 5 minutes to begin 3 BP measurements – research staff was trained to push start button and leave exam room during the 5 minute delay and measurements, during which time participant refrained from talking.
Geriatric Outcome Measures

- **Assessments**
  - Gait speed – 4 m walk
- **Frailty status**
- **Cognitive battery and brain MRI – SPRINT-MIND**
- **Adverse Events**
  - PHQ-9 and Health Related Quality of Life
  - Falls and injurious falls
  - Orthostatic hypotension +/- dizziness
  - Hospitalizations and Nursing home placement
Frailty Index

- Deficit accumulation approach
- Assess a large number of aging-related deficits, usually at least 30 deficits
- Scores range from 0 to 1 – higher values denote more deficits
- Values > 0.7 not observed

Relationship of FI with Age

- Single dash lines: Estimates from National Long Term Care Survey

Relationship of SPRINT Cohort FI with Age

- Single dash lines: Estimates from National Long Term Care Survey
  Kulminski et al. Mech Ageing Dev 2006;127:840-8

- Double dash lines: 10-year mean FI values from Survey of Health, Ageing and Retirement in Europe (SHARE)

- Solid lines: Fit based on local polynomial regression in SPRINT with 95% CIs (shaded areas)
Adverse Events by Frailty Status

### Baseline Characteristics: Participants 75 years or older

<table>
<thead>
<tr>
<th></th>
<th>Intensive N=1,317</th>
<th>Standard N=1,319</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>79.8 ± 3.9</td>
<td>79.9 ± 4.1</td>
<td>0.405</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>499 (37.9)</td>
<td>501 (38)</td>
<td>0.992</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td>0.879</td>
</tr>
<tr>
<td>White</td>
<td>977 (74.2)</td>
<td>987 (74.8)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>225 (17.1)</td>
<td>226 (17.1)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>89 (6.8)</td>
<td>85 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>26 (2)</td>
<td>21 (1.6)</td>
<td></td>
</tr>
<tr>
<td>History of CVD</td>
<td>338 (25.7)</td>
<td>309 (23.4)</td>
<td>0.197</td>
</tr>
<tr>
<td>10-year Framingham risk (%)</td>
<td>24.2 (16.8-32.8)</td>
<td>25 (17-33.4)</td>
<td>0.475</td>
</tr>
<tr>
<td>Number of antihypertensive meds</td>
<td>1.9 ± 1</td>
<td>1.9 ± 1</td>
<td>0.173</td>
</tr>
<tr>
<td>Baseline blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>141.6 ± 15.7</td>
<td>141.6 ± 15.8</td>
<td>0.986</td>
</tr>
<tr>
<td>Diastolic</td>
<td>71.5 ± 11</td>
<td>70.9 ± 11</td>
<td>0.177</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>27.8 ± 4.9</td>
<td>27.7 ± 4.6</td>
<td>0.464</td>
</tr>
<tr>
<td>eGFR (CKD-EPI, ml/min/1.73m²)</td>
<td>61.4 ± 17</td>
<td>61.2 ± 16.7</td>
<td>0.764</td>
</tr>
<tr>
<td>eGFR&lt;60 ml/min/1.73m²</td>
<td>614 (46.9)</td>
<td>608 (46.4)</td>
<td>0.859</td>
</tr>
<tr>
<td>Urine albumin / creatinine (mg/g)</td>
<td>13 (7.2-31.6)</td>
<td>13.4 (7.2-33.4)</td>
<td>0.505</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>181.4 ± 39</td>
<td>181.8 ± 38.7</td>
<td>0.767</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>97.9 ± 12.1</td>
<td>98.2 ± 11.6</td>
<td>0.606</td>
</tr>
</tbody>
</table>

Values are N (%), mean ± SD, or median (IQR)
Baseline Characteristics: Participants 75 years or older

<table>
<thead>
<tr>
<th></th>
<th>Intensive N=1,317</th>
<th>Standard N=1,319</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait speed (m/s)</td>
<td>0.90 (0.77-1.05)</td>
<td>0.92 (0.77-1.06)</td>
<td>0.375</td>
</tr>
<tr>
<td>Gait speed &lt;0.8 m/s</td>
<td>371 (29.7)</td>
<td>369 (29.2)</td>
<td>0.853</td>
</tr>
<tr>
<td>Frailty Index</td>
<td>0.18 (0.13-0.23)</td>
<td>0.17 (0.12-0.22)</td>
<td>0.004</td>
</tr>
<tr>
<td>Frailty Status</td>
<td></td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>Fit (FI≤0.10)</td>
<td>159 (12.1)</td>
<td>190 (14.5)</td>
<td></td>
</tr>
<tr>
<td>Less fit (0.10&lt;FI≤0.21)</td>
<td>711 (54.3)</td>
<td>745 (56.9)</td>
<td></td>
</tr>
<tr>
<td>Frail (FI&gt;0.21)</td>
<td>440 (33.6)</td>
<td>375 (28.6)</td>
<td></td>
</tr>
<tr>
<td>MoCA score (0 to 30)</td>
<td>22 (19-25)</td>
<td>22 (19-25)</td>
<td>0.701</td>
</tr>
<tr>
<td>VR-12 Physical Component Summary Score</td>
<td>43.8 ± 10.2</td>
<td>44.3 ± 9.8</td>
<td>0.242</td>
</tr>
<tr>
<td>VR-12 Mental Component Summary Score</td>
<td>54.8 ± 8.5</td>
<td>55.3 ± 8.2</td>
<td>0.135</td>
</tr>
</tbody>
</table>

(MoCA) Montreal Cognitive Assessment
(VR-12) Veteran's RAND 12-item Health Survey
Values are N (%), mean ± SD, or median (IQR)
Systolic BP During Follow-up

Delta SBP: 11.4 mmHg (95% CI: 10.8 to 11.9 mmHg)

Standard-treatment
134.8 mmHg
95% CI (134.3, 135.)

Intensive-treatment
123.4 mmHg
95% CI (123.0, 123.9)

# of classes of antihypertensive meds

# of Participants

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Primary outcome includes non-fatal myocardial infarction (MI), acute coronary syndrome not resulting in MI, non-fatal stroke, non-fatal acute decompensated heart failure, and CVD death.
Cumulative Hazards for SPRINT Primary Outcome by Frailty Status

- **Fit**
  - Standard: 190
  - Intensive: 159
  - HR: 0.47 (95% CI: 0.13 to 1.39)

- **Less Fit**
  - Standard: 745
  - Intensive: 711
  - HR: 0.63 (95% CI: 0.43 to 0.91)

- **Frail**
  - Standard: 375
  - Intensive: 440
  - HR: 0.68 (95% CI: 0.45 to 1.01)
Cumulative Hazards for SPRINT Primary Outcome by Gait Speed

Gait Speed 0.8 m/s or greater
- Standard-treatment
- Intensive-treatment

HR: 0.67 (95% CI: 0.47 to 0.94)

Gait Speed <0.8 m/s
- Standard-treatment
- Intensive-treatment

HR: 0.63 (95% CI: 0.40 to 0.99)
**SPRINT Follow-up Experience:**
Withdrawn Consent & Loss to Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Intensive-treatment</th>
<th>Standard-treatment</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%/year</td>
<td>N</td>
<td>%/year</td>
</tr>
<tr>
<td>Overall</td>
<td>62</td>
<td>1.55 (1.21, 1.99)</td>
<td>64</td>
<td>1.62 (1.27, 2.07)</td>
</tr>
<tr>
<td>Frailty Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit</td>
<td>2</td>
<td>0.41 (0.10, 1.62)</td>
<td>4</td>
<td>0.69 (0.26, 1.85)</td>
</tr>
<tr>
<td>Less fit</td>
<td>31</td>
<td>1.43 (1.01, 2.03)</td>
<td>33</td>
<td>1.47 (1.04, 2.06)</td>
</tr>
<tr>
<td>Frail</td>
<td>26</td>
<td>1.97 (1.34, 2.89)</td>
<td>22</td>
<td>1.98 (1.30, 3.00)</td>
</tr>
<tr>
<td>Gait Speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥0.8 m/s</td>
<td>37</td>
<td>1.38 (1.00, 1.91)</td>
<td>35</td>
<td>1.29 (0.93, 1.80)</td>
</tr>
<tr>
<td>&lt;0.8 m/s</td>
<td>20</td>
<td>1.81 (1.17, 2.81)</td>
<td>24</td>
<td>2.20 (1.47, 3.28)</td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>2.38 (0.99, 5.71)</td>
<td>5</td>
<td>3.08 (1.28, 7.41)</td>
</tr>
</tbody>
</table>

(%/year) Percentage of participants withdrawing consent or lost to follow-up per year. (HR) Hazard Ratio based on competing risks model accounting for death.
SPRINT Follow-up Experience: Withdrawn Consent & Loss to Follow-up

(%/year) Percentage of participants withdrawing consent or lost to follow-up per year. (HR) Hazard Ratio based on competing risks model accounting for death.
Serious Adverse Events, by treatment group in SPRINT participants > 75 years

All p>0.05

Intensive-treatment
Standard-treatment

% of participants experiencing at least one SAE

Overall: 48.4% vs. 48.3%
Fit: 31.4% vs. 34.7%
Less Fit: 46.8% vs. 45.8%
Frail: 57% vs. 60.5%
≥ 0.8 m/s: 47.6% vs. 46.1%
<0.8 m/s: 50.4% vs. 52.8%

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## Conditions of Interest for Participants > 75 Years

<table>
<thead>
<tr>
<th>Conditions of Interest</th>
<th>Intensive-treatment</th>
<th>Standard-treatment</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N with event (%)</td>
<td>N with event (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>214 (16.2)</td>
<td>190 (14.4)</td>
<td>1.18 (0.97, 1.44)</td>
<td>0.106</td>
</tr>
<tr>
<td>Syncope</td>
<td>32 (2.4)</td>
<td>19 (1.4)</td>
<td>1.71 (0.97, 3.09)</td>
<td>0.066</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>39 (3.0)</td>
<td>32 (2.4)</td>
<td>1.23 (0.76, 2.00)</td>
<td>0.401</td>
</tr>
<tr>
<td>Electrolyte Abnormality</td>
<td>53 (4.0)</td>
<td>36 (2.7)</td>
<td>1.51 (0.99, 2.33)</td>
<td>0.058</td>
</tr>
<tr>
<td>Injurious Fall</td>
<td>65 (4.9)</td>
<td>73 (5.5)</td>
<td>0.91 (0.65, 1.29)</td>
<td>0.605</td>
</tr>
<tr>
<td>Acute Kidney Injury or Acute Renal Failure</td>
<td>72 (5.5)</td>
<td>53 (4.0)</td>
<td>1.41 (0.98, 2.04)</td>
<td>0.061</td>
</tr>
</tbody>
</table>
Conditions of Interest for Participants > 75 Years

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intensive-treatment</th>
<th>Standard-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>2.4%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Syncope</td>
<td>3%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2.9%</td>
<td>3%</td>
</tr>
<tr>
<td>Electrolyte Abnormality</td>
<td>4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Injurious Fall</td>
<td>4.9%</td>
<td>5.5%</td>
</tr>
<tr>
<td>AKI / ARF</td>
<td>5.5%</td>
<td>4%</td>
</tr>
</tbody>
</table>
Conditions of Interest for Participants > 75 Years By Frailty Status and Gait Speed
Number of Participants with a Monitored Clinical Measure During Follow-up

<table>
<thead>
<tr>
<th>Monitored Clinical Events</th>
<th>Intensive-treatment N with event (%)</th>
<th>Standard-treatment N with event (%)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory Measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium&lt;130 mmol/L</td>
<td>69 (5.2)</td>
<td>45 (3.4)</td>
<td>1.56 (1.07, 2.30)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sodium&gt;150 mmol/L</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Potassium&lt;3 mmol/L</td>
<td>17 (1.3)</td>
<td>11 (0.8)</td>
<td>1.50 (0.69, 3.37)</td>
<td>0.303</td>
</tr>
<tr>
<td>Potassium&gt;5.5 mmol/L</td>
<td>69 (5.2)</td>
<td>65 (4.9)</td>
<td>1.01 (0.71, 1.42)</td>
<td>0.972</td>
</tr>
<tr>
<td>Signs and Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>277 (21.0)</td>
<td>288 (21.8)</td>
<td>0.90 (0.76, 1.07)</td>
<td>0.241</td>
</tr>
<tr>
<td>Orthostatic hypotension with dizziness</td>
<td>25 (1.9)</td>
<td>17 (1.3)</td>
<td>1.44 (0.77, 2.73)</td>
<td>0.252</td>
</tr>
</tbody>
</table>
Generalizability

Who may benefit?
Conclusions

- The SPRINT-Senior cohort is representative of community dwelling older adults.
- Rates of hypotension, syncope, electrolyte abnormalities, kidney injury were higher in the intensive arm, but not rates of injurious falls or orthostatic hypotension.
- Overall, benefits of more intensive BP lowering – 33% reduction in primary CV outcome and 32% reduction in total mortality – exceeded the potential for harm, even among the most frail older patients.
Acknowledgements

- 9,361 volunteers who agreed to participate in SPRINT
- Investigators and staff, including Steering Committee, other principals at the 5 Clinical Center Networks, 102 participating Clinical Centers, Coordinating Center, Central Laboratory, ECG Reading Center, MRI Reading Center, and Drug Distribution Center
- National Institutes of Health
  - National Heart, Lung, and Blood Institute (NHLBI)
  - National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
  - National Institute on Aging (NIA)
  - National Institute of Neurological Disorders and Stroke (NINDS)
- SPRINT Data and Safety Monitoring Board (DSMB)
- Takeda and Arbor Pharmaceuticals (donated 5% of medication used)
Acknowledgements

Nicholas M. Pajewski, PhD

Questions...
Forthcoming SPRINT Results

- SPRINT-MIND Cognitive and brain MRI outcomes
- Renal
- Health related quality of life
- Adverse events (nursing home placement), safety (falls, orthostasis), cost analysis
Healthy age 60 to 80+: What SBP Target?

1991 - 2015

SHEP
HYVET
JNC7
JNC8
SPRINT

100 110 120 130 140 150 160 170 180

AHA 2016

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Caveats

- Exclusions:
  - Diabetes, stroke, heart failure
  - Standing BP < 110 mm Hg
  - Community living, ambulatory

- BP measurement protocol
Frailty Status in HYVET

- Frailty index distribution in HYVET matches general population > 80 years
- No evidence interaction between effect of treatment and frailty
- “Both the frailer and the fitter older adults with hypertension appeared to gain from treatment.”

Frailty index adjusted treatment effects (n=2,656)

<table>
<thead>
<tr>
<th></th>
<th>Stroke</th>
<th>CV Events</th>
<th>Total Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratios (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0.64</td>
<td>0.59</td>
<td>0.83</td>
</tr>
<tr>
<td>(0.42–0.96)</td>
<td>(0.45–0.77)</td>
<td>(0.66–1.04)</td>
<td></td>
</tr>
</tbody>
</table>