TREATMENT OF GERIATRIC HYPERTENSION: THE SPRINT TRIAL AND RECENT GUIDELINES

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DISCLOSURES

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☐ No relevant financial relationships with any commercial interests to report
1. Epidemiology and Historical Prologue
2. The Evolving Systolic Blood Pressure Target for Geriatric Hypertension
   a. SHEP – 1991
   b. HYVET – 2008
   c. SPRINT – 2015
3. Rates of uncontrolled hypertension
4. Summary and Conclusions
BLOOD PRESSURE BY AGE AND SEX

Figure 1. Mean Blood Pressure According to Age and Race or Ethnic Group in U.S. Adults. Data are from Burt et al.8

RMGC August 2017
Chobanian, NEJM 357, 2007
PREVALENCE OF HYPERTENSION: AGE AND SEX

Men
Women

RMGC August 2017  American Heart Association
HISTORICAL PROLOGUE – 1

1733
• Stephen Hales measures blood pressure

1937
• “...the treatment of the hypertension itself is a difficult and almost hopeless task ... we know that in advanced cases with permanently narrowed coronary and cerebral arteries the hypertension may be an important compensatory mechanism which should not be tampered with.” White, PD. Heart Disease. 2nd ed. NY Macmillan, 1937:326

1945
• FDR dies April 12, 1945
FRANKLIN DELANO ROOSEVELT

- Cause of Death – Hemorrhagic Stroke due to Malignant Hypertension
- February, 1945 - BP 260 / 150 mmHg
- Medications - Digitalis, Phenobarbital

April 12, 1945
HISTORICAL PROLOGUE – 2

1950 -1956
• Chemotherapy of hypertension
• hexamethonium bromide and reserpine

1959 -1960
• Hydrochlorothiazide (HCTZ; 1959) and chlorthalidone (1960) approved
1. Epidemiology and Historical Prologue

2. The Evolving Systolic Blood Pressure Target for Geriatric Hypertension
   a. SHEP – 1991
   b. HYVET – 2008
   c. SPRINT – 2015

3. Uncontrolled hypertension

4. Summary and Conclusions
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
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.
Objective: To assess the ability of antihypertensive drug treatment to reduce the risk of nonfatal and fatal (total) stroke in isolated systolic hypertension.
SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM (SHEP) – 1991

35% reduction in stroke rate

![Graph showing 35% reduction in stroke rate between Placebo and Active groups.](image)

Fig 2.—Cumulative fatal plus nonfatal stroke rate per 100 participants in the active treatment (solid line) and placebo (broken line) groups during the Systolic Hypertension in the Elderly Program.
TREATING HYPERTENSION REDUCES CARDIOVASCULAR RISK AND MORTALITY

Psaty et al.; JAMA 289: 2534, 2003
JNC 7, 2003

• Treatment of hypertension in older persons has demonstrated major benefits.

• “Treatment recommendations for older individuals with hypertension should follow the same principles for the general care of hypertension.”

• i.e. a SBP target of 140 mm Hg
WHAT ABOUT OCTOGENARIANS?
HYPERTENSION IN THE VERY ELDERLY TRIAL

- International, multi-center, randomized double-blind placebo controlled trial
- **Study Aim:** to establish the risk and benefits of hypertension treatment in those over age 80
CONCLUSIONS

- Treatment to SBP < 150 mm Hg reduced stroke and total mortality
- NNT (2 years) = 94 for stroke and 40 for mortality
- Large and significant benefit in reduction of heart failure and for combined cardiovascular events
- Treatment regimen was safe
HYVET CONCLUSION

“The results of HYVET prove that it is not too late to start antihypertensive therapy in older people and expands the upper limit of the age spectrum for which there is evidence from clinical trials of a treatment benefit.”

The panel agreed that more research is needed to identify optimal goals of SBP…”

JNC 8

Equipoise

Systolic Blood Pressure Intervention Trial (SPRINT)
Randomized controlled clinical trial to examine effect of more intensive high blood pressure treatment strategy than is currently recommended

Target Systolic BP

- **Intensive Treatment**
  - Goal SBP < 120 mm Hg
- **Standard Treatment**
  - Goal SBP < 140 mm Hg

SPRINT design details available at:
- ClinicalTrials.gov (NCT01206062)
SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL (SPRINT)

- JD Williamson and Coauthors for the SPRINT Research Group
- Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years: A Randomized Clinical Trial
- Published May 19, 2016
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

• 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
  - 10% of screened patients excluded due to this
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
## 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><strong>Age (years)</strong></td>
<td>79.8 ± 3.9</td>
<td>79.9 ± 4.1</td>
<td>0.405</td>
</tr>
<tr>
<td><strong>Gender (female)</strong></td>
<td>499 (37.9)</td>
<td>501 (38)</td>
<td>0.992</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></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><strong>History of CVD</strong></td>
<td>338 (25.7)</td>
<td>309 (23.4)</td>
<td>0.197</td>
</tr>
<tr>
<td><strong>10-year Framingham risk (%)</strong></td>
<td>24.2 (16.8-32.8)</td>
<td>25 (17-33.4)</td>
<td>0.475</td>
</tr>
<tr>
<td><strong>Number of antihypertensive meds</strong></td>
<td>1.9 ± 1</td>
<td>1.9 ± 1</td>
<td>0.173</td>
</tr>
<tr>
<td><strong>Baseline blood pressure (mmHg)</strong></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><strong>Body Mass Index (kg/m²)</strong></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><strong>Urine albumin / creatinine (mg/g)</strong></td>
<td>13 (7.2-31.8)</td>
<td>13.4 (7.2-33.4)</td>
<td>0.505</td>
</tr>
<tr>
<td><strong>Total cholesterol (mg/dL)</strong></td>
<td>181.4 ± 39</td>
<td>181.8 ± 38.7</td>
<td>0.767</td>
</tr>
<tr>
<td><strong>Fasting plasma glucose (mg/dL)</strong></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

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<th>p-value</th>
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</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
- Intensive

HR: 0.47 (95% CI: 0.13 to 1.39)

Less Fit
- Standard
- Intensive

HR: 0.63 (95% CI: 0.43 to 0.91)

Frail
- Standard
- Intensive

HR: 0.68 (95% CI: 0.45 to 1.01)
CUMULATIVE HAZARDS FOR SPRINT PRIMARY OUTCOME BY GAIT SPEED

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

HR: 0.63 (95% CI: 0.40 to 0.99)
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.

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CONDITIONS OF INTEREST FOR PARTICIPANTS > 75 YEARS

% of Participants Experiencing at Least One Condition of Interest

- Hypotension: 2.4% (Intensive-treatment), 1.4% (Standard-treatment)
- Syncope: 3% (Intensive-treatment), 2.4% (Standard-treatment)
- Bradycardia: 2.9% (Intensive-treatment), 3% (Standard-treatment)
- Electrolyte Abnormality: 4% (Intensive-treatment), 2.7% (Standard-treatment)
- Injurious Fall: 5.5% (Intensive-treatment), 5.5% (Standard-treatment)
- AKI / ARF: 4% (Intensive-treatment), 4% (Standard-treatment)
ACUTE DECOMPENSATED HEART FAILURE OUTCOME BY TREATMENT GROUP
Effect of Intensive Blood-Pressure Treatment on Patient-Reported Outcomes

Dan R. Berlowitz, M.D., M.P.H., Capri G. Foy, Ph.D., Lewis E. Kazis, Sc.D., Linda P. Bolin, Ph.D., R.N., Molly B. Conroy, M.D., M.P.H., Peter Fitzpatrick, M.D., Tanya R. Gure, M.D., Paul L. Kimmel, M.D., Kent Kirchner, M.D., Donald E. Morisky, Sc.D., M.S.P.H., Jill Newman, M.S., Christine Olney, Ph.D., R.N., Suzanne Oparil, M.D., Nicholas M. Pajewski, Ph.D., James Powell, M.D., Thomas Ramsey, Ph.D., M.B.A., Debra L. Simmons, M.D., Joni Snyder, M.A., Mark A. Supiano, M.D., Daniel E. Weiner, M.D., and Jeff Whittle, M.D., for the SPRINT Research Group*

CONCLUSIONS
Patient-reported outcomes among participants who received intensive treatment, which targeted a systolic blood pressure of less than 120 mm Hg, were similar to those among participants who received standard treatment, including among participants with decreased physical or cognitive function. (Funded by the National Institutes of Health; SPRINT ClinicalTrials.gov number, NCT01206062.)

N Engl J Med 2017;377:733-44
HEALTH RELATED QUALITY OF LIFE – 2

N Engl J Med 2017;377:733-44
FIGURE S4. Veterans RAND 12 Item Health Survey (VR-12) scores over the course of follow-up by treatment group and frailty status.
Cost-Effectiveness of Intensive versus Standard Blood-Pressure Control


CONCLUSIONS
In this simulation study, intensive systolic blood-pressure control prevented cardiovascular disease events and prolonged life and did so at levels below common willingness-to-pay thresholds per QALY, regardless of whether benefits were reduced after 5 years or persisted for the patient’s remaining lifetime. (Funded by the National Heart, Lung, and Blood Institute and others; SPRINT ClinicalTrials.gov number, NCT01206062.)
In the best-case scenario in which adherence and treatment effects persisted over the patient’s lifetime, intensive control cost approximately $28,000 per QALY gained.

The probability that intensive control was cost-effective increased to 79% at $50,000 per QALY and to 93% at $100,000 per QALY.
COST EFFECTIVENESS – 3

Simulated Life of 52-Year-Old Woman

- Adherent to medication

- Standard

- Intensive

Age

50 55 60 65 70 75 80 85 90

Stroke

Hypotension  Acute Kidney Injury

Total Cost $271,000

Total Cost $423,000

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August 2017
APPLYING THE SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL RESULTS TO OLDER ADULTS

• Why are the SPRINT results discordant from those of epidemiological studies?

• Do the SPRINT findings generalize to the frail, older adults that I care for?

• What are future considerations, and how low should we go?

Supiano & Williamson JAGS, 2016
## COMPARING RCT TO USUAL CARE

<table>
<thead>
<tr>
<th></th>
<th>Usual Care</th>
<th>Randomized Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP measurement</strong></td>
<td>• Manual aneroid or digital sphygmomanometer</td>
<td>• Automated office BP device</td>
</tr>
<tr>
<td></td>
<td>• Single reading</td>
<td>• Observer independent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Serial readings</td>
</tr>
<tr>
<td><strong>Orthostatic BP readings</strong></td>
<td>• Only symptom driven</td>
<td>• Routinely assessed</td>
</tr>
<tr>
<td><strong>BP monitoring visits</strong></td>
<td>• Physician directed</td>
<td>• Team approach</td>
</tr>
<tr>
<td></td>
<td>• No set frequency</td>
<td>• Protocol directed: monthly x 3, then every 3 months</td>
</tr>
<tr>
<td></td>
<td>• Target often not clearly established</td>
<td>• Standardized protocol to meet defined target</td>
</tr>
<tr>
<td><strong>Medication management</strong></td>
<td>• Drug costs borne by patients</td>
<td>• Free medications</td>
</tr>
<tr>
<td></td>
<td>• Adherence not always monitored</td>
<td>• Strict adherence checks</td>
</tr>
<tr>
<td><strong>Medication titration</strong></td>
<td>• Ad lib</td>
<td>• Standardized protocol</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>• Not routinely assessed</td>
<td>• Close monitoring</td>
</tr>
</tbody>
</table>
Who may benefit?

GENERALIZABILITY

REDUCE YOUR BP TARGET, REDUCE YOUR RISK

The new findings from the Systolic Blood Pressure Intervention Trial show lowering systolic blood pressure to 120 (below current guidelines of 140 or 150) significantly reduces risk for heart attack, heart failure and death among those at high risk for heart disease.

How many adults 75 years of age and older in the U.S. could the findings of this study affect?

219.4 MILLION

The number of adults living in the U.S.

5.8 MILLION

Most likely to benefit*

16.7 MILLION

Number of adults age 75 or older

9.1 MILLION

Adults 75 or older with elevated blood pressure** who are at high risk for heart disease

*Adults age 75 or older with a systolic blood pressure ≥130 mmHg, at high risk for heart disease who do not have diabetes, history of stroke, or severe kidney disease — Including diastolic ≥130 mmHg

Generalizability of results from the Systolic Blood Pressure Intervention Trial (SPRINT) to the U.S. adult population

Journal of the American College of Cardiology, online, No. 9, 2015.

RMGC August 2017
WHAT LIES AHEAD?

- SPRINT-MIND: cognitive and brain MRI outcomes
- SPRINT Alzheimer’s, Senior, Kidney (ASK)
  - NIA-funded one year extension
  - Data (cognitive battery and creatinine) collection – September 2017 to February 2018
  - Results to follow…
HEALTHY AGE 60 TO 80+: WHAT SBP TARGET?

100 110 120 130 140 150 160 170 180

SHEP

HYVET

JNC7

JNC8

SPRINT

AHA


RMGC August 2017

JNC7

JNC8

AHA

2017
OUTLINE

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3. Rates of uncontrolled hypertension
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SBP TRENDS AMONG 60 TO 74 YEAR OLDS: 1959 TO 2010
ANTI-HYPERTENSIVE RX NON-ADHERENCE RATES
RATES OF UNCONTROLLED HYPERTENSION

Figure 9. Uncontrolled high blood pressure among adults aged 20 and over with hypertension, by sex and age: United States, 1988–1994 through 2009–2012

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CDC/NCHS, Health, United States, 2014; Data from NHANES
UNCONTROLLED HYPERTENSION IS A MAJOR PUBLIC HEALTH CONCERN

• “Only half of Americans with hypertension have BP < 140/90 mm Hg”
• 13% (9 million) have SBP > 160 mm Hg
• Million hearts program – prevent 1 million strokes and heart attacks by 2017
  – http://millionhearts.hhs.gov
• “… no debate about the need to improve performance and the important role of protocol-driven care”

Frieden et al; JAMA 311:21; 2014
SUMMARY AND CONCLUSIONS

- A SBP target of < 140 mm Hg is appropriate for most healthy people 60-80 years of age
- A benefit-based SBP target of < 120 mm Hg may be appropriate for those at high CVD risk
- Additional follow-up is needed to assess CKD and cognitive outcomes of intensive therapy
- Much work is needed to improve BP control rates
ACKNOWLEDGEMENTS

• Research Support
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  – VA Salt Lake City GRECC

• Collaborators
  – Utah CCN
    • Alfred Cheung
    • Jeff Childs
  – BU Vascular Lab – Joe Vita
  – Wake Forest CC – Walter Ambrosius

• Utah CCN sites
  – U Chicago
  – Denver
  – GWU
  – Pittsburgh
  – Stanford
  – Tufts
  – UTSW
  – Utah
  – UCSD
  – Vanderbilt
  – Houston VA
“The secret to living well and longer is to eat half, walk double, laugh triple, and love without measure.”
QUESTIONS...

About our logo...

The bristlecone pine tree (Pinus longaeva) - the earth’s oldest inhabitant with a life span of 4,000 years - is found only in Utah and five other western states. Its extraordinary longevity and ability to adapt and survive in extremely harsh environmental conditions above 10,000 feet embodies the investigative spirit and mission of the Utah Center on Aging.

@Aging_MD and @utahgeriatrics