Systolic Blood Pressure Intervention Trial (SPRINT)  
What does it mean for clinical practice?

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- Observational studies identify strong association between BP and risk of CVD, with no evidence of threshold for the relationship

- High BP very common
  - High SBP leading risk factor for mortality and disability-adjusted life years
  - Worldwide, >1 billion adults have hypertension

- Clinical trials demonstrate antihypertensive drug therapy reduces risk of CVD

- However, optimal target for SBP lowering uncertain:
  - ACCORD trial in diabetic patients raised concerns that lower BP targets may not be appropriate in all patients
SPRINT Research Question

Examine effect of more intensive high blood pressure treatment than is currently recommended

Randomized Controlled Trial

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)
Major Inclusion Criteria

- ≥50 years old
- **Systolic blood pressure**: 130 – 180 mm Hg (treated or untreated)
- **Additional cardiovascular disease (CVD) risk**
  
  - Clinical or subclinical CVD (excluding stroke)
  - Chronic kidney disease (CKD), defined as eGFR 20 – <60 ml/min/1.73m²
  - Framingham Risk Score for 10-year CVD risk ≥ 15%
  - Age ≥ 75 years

**NOTE: TRIAL EXCLUDED DIABETIC PATIENTS**
Major Exclusion Criteria

- Stroke
- Diabetes mellitus
- Polycystic kidney disease
- Congestive heart failure (symptoms or EF < 35%)
- Proteinuria >1g/d
- CKD with eGFR < 20 mL/min/1.73m² (MDRD)
- Adherence concerns
Major Exclusion Criteria

- Stroke
- *Diabetes mellitus*
- Polycystic kidney disease
- Congestive heart failure (symptoms or EF < 35%)
- Proteinuria >1g/d
- CKD with eGFR < 20 mL/min/1.73m² (MDRD)
- Adherence concerns
SPRINT: Enrollment and Follow-up Experience

Screened (N=14,692)

Randomized (N=9,361)

Intensive Treatment (N=4,678)

Standard Treatment (N=4,683)

Analyzed (Intention to treat) 4,678 4,683
## Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total N=9361</th>
<th>Intensive N=4678</th>
<th>Standard N=4683</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD) age, years</strong></td>
<td>67.9 (9.4)</td>
<td>67.9 (9.4)</td>
<td>67.9 (9.5)</td>
</tr>
<tr>
<td>% ≥75 years</td>
<td>28.2%</td>
<td>28.2%</td>
<td>28.2%</td>
</tr>
<tr>
<td>Female, %</td>
<td>35.6%</td>
<td>36.0%</td>
<td>35.2%</td>
</tr>
<tr>
<td>White, %</td>
<td>57.7%</td>
<td>57.7%</td>
<td>57.7%</td>
</tr>
<tr>
<td>African-American, %</td>
<td>29.9%</td>
<td>29.5%</td>
<td>30.4%</td>
</tr>
<tr>
<td>Hispanic, %</td>
<td>10.5%</td>
<td>10.8%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Prior CVD, %</td>
<td>20.1%</td>
<td>20.1%</td>
<td>20.0%</td>
</tr>
<tr>
<td>Mean 10-year Framingham CVD risk, %</td>
<td>20.1%</td>
<td>20.1%</td>
<td>20.1%</td>
</tr>
<tr>
<td>Taking antihypertensive meds, %</td>
<td>90.6%</td>
<td>90.8%</td>
<td>90.4%</td>
</tr>
<tr>
<td>Mean (SD) number of antihypertensive meds</td>
<td>1.8 (1.0)</td>
<td>1.8 (1.0)</td>
<td>1.8 (1.0)</td>
</tr>
<tr>
<td>Mean (SD) Baseline BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>139.7 (15.6)</td>
<td>139.7 (15.8)</td>
<td>139.7 (15.4)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78.1 (11.9)</td>
<td>78.2 (11.9)</td>
<td>78.0 (12.0)</td>
</tr>
</tbody>
</table>
## Selected Baseline Laboratory Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (N=9361)</th>
<th>Intensive (N=4678)</th>
<th>Standard (N=4683)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD) eGFR, mL/min/1.73 m²</strong></td>
<td>71.7 (20.6)</td>
<td>71.8 (20.7)</td>
<td>71.7 (20.5)</td>
</tr>
<tr>
<td><strong>% with eGFR&lt;60 mL/min/1.73m²</strong></td>
<td>28.3</td>
<td>28.4</td>
<td>28.1</td>
</tr>
<tr>
<td><strong>Mean (SD) Urine albumin/creatinine, mg/g</strong></td>
<td>42.6 (166.3)</td>
<td>44.1 (178.7)</td>
<td>41.1 (152.9)</td>
</tr>
<tr>
<td><strong>Mean (SD) Total cholesterol, mg/dL</strong></td>
<td>190.1 (41.2)</td>
<td>190.2 (41.4)</td>
<td>190.0 (40.9)</td>
</tr>
<tr>
<td><strong>Mean (SD) Fasting plasma glucose, mg/dL</strong></td>
<td>98.8 (13.5)</td>
<td>98.8 (13.7)</td>
<td>98.8 (13.4)</td>
</tr>
</tbody>
</table>
Pre-specified Subgroups of Special Interest

- Age (<75 vs. ≥75 years)
- Gender (Men vs. Women)
- Race/ethnicity (African-American vs. Non African-American)
- CKD (eGFR <60 vs. ≥60 mL/min/1.73m²)
- CVD (CVD vs. no prior CVD)
- Level of BP (Baseline SBP tertiles: ≤132, 133 to 144, ≥145 mm Hg)
Primary Outcome and Primary Hypothesis

• **Primary outcome**
  – CVD composite: first occurrence of
    • Myocardial infarction (MI)
    • Acute coronary syndrome (non-MI ACS)
    • Stroke
    • Acute decompensated heart failure (HF)
    • Cardiovascular disease death

• **Primary hypothesis***
  • CVD composite event rate lower in intensive compared to standard treatment

*Estimated power of 88.7% to detect a 20% difference
- based on recruitment of 9,250 participants, 4-6 years of follow-up and loss to follow-up of 2%/year.
Additional Outcomes

- All-cause mortality
- Primary outcome + all-cause mortality
- Renal
  - Main secondary outcome:
    - Participants with CKD at baseline: incidence of decline in eGFR ≥50% or ESRD
  - Additional secondary outcomes:
    - Participants without CKD at baseline: incidence of decline in eGFR ≥30% (to <60 mL/min/1.73m²)
    - Participants with or without CKD at baseline: Incidence of albuminuria
BP Intervention

• **BP monitored monthly for 3 months and every 3 months thereafter (additional visits could be scheduled)**

• **Antihypertensive medication titration decisions based on mean BP (3 readings at each visit), using a structured stepped-care approach**

• **Agents from all major antihypertensive drug classes available free of charge**

• **Periodic assessment for orthostatic hypotension and related symptoms**
Start Here: At randomization visit, begin with 2 or 3 drug therapy* using a combination of a thiazide-type diuretic, and/or an ACEI or ARB (but not both) and/or a CCB

Include β-blocker or other agents as appropriate for compelling indication

Monitor as Designated Through Follow-up

You must:
A) Add Therapy Not Already in Use**

AND

B) See participant monthly until SBP <120 mm Hg

Is SBP ≥120 mm Hg at this visit?

Yes

Is this a milestone visit?

Yes

You must:
A) Titrate or Add Therapy Not Already in Use**

AND

No

B) See participant monthly until SBP <120 mm Hg

Is DBP ≥100 mm Hg at this visit or is DBP ≥90 mm Hg on last two visits?

No

Continue therapy

Yes

You must:
A) Titrate or Add Therapy Not Already in Use**

* May begin with a single agent for participants 75 years old or older with SBP < 140 on 0-1 meds at study entry.

A second medication should be added at the 1-month visit if participant is asymptomatic and SBP ≥ 130.

** May use loop diuretic for participants with advanced CKD

† Unless side effects warrant change in therapy

†† Consider consulting with the Clinical Center Network before adding a fifth anti-hypertensive medication

* Or until clinical decision made that therapy should not be increased further
**SPRINT Treatment Algorithm**

**Standard Treatment**

**Start Here:** Convert to SPRINT medication, if indicated; randomization visit is first visit that should be considered in 2-visit criteria

- **Is SBP ≥160 mm Hg at this visit or ≥140 mm Hg on 2 consecutive protocol visits?**
  - **Yes**
    - **Titrate or Add Therapy Not Already in Use**
    - Schedule 1 month PRN visit when SBP ≥160 mm Hg
  - **No**

- **Is DBP ≥100 mm Hg at this visit or ≥90 mm Hg on 2 consecutive protocol visits?**
  - **Yes**
    - **Titrate or Add Therapy Not Already in Use**
  - **No**

- **Is SBP <130 mm Hg at this visit or <135 mm Hg on 2 consecutive protocol visits?**
  - **Yes**
    - **Step down**
  - **No**
    - **Continue therapy**

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- Include β-blocker or other agents as appropriate for compelling indications
- Unless side effects warrant change in therapy
- Consider consulting with the Clinical Center Network before adding a fifth anti-hypertensive medication.
Systolic BP During Follow-up

Year 1

Mean SBP 136.2 mm Hg

Mean SBP 121.4 mm Hg

Standard

Intensive

Standard: 134.6 mm Hg

Intensive: 121.5 mm Hg

Average number of antihypertensive medications

Number of participants
Decision to Stop BP Intervention

- On August 20th, 2015, NHLBI Director accepted DSMB recommendation to inform SPRINT investigators and participants of CVD results

- Concurrently, decision made to stop BP intervention

- Median follow-up = 3.26 years
Hazard Ratio = 0.75 (95% CI: 0.64 to 0.89)

SPRINT Primary Outcome
Cumulative Hazard

During Trial (median follow-up = 3.26 years)
Number Needed to Treat (NNT) to prevent a primary outcome = 61
## SPRINT Primary Outcome and its Components

### Event Rates and Hazard Ratios

<table>
<thead>
<tr>
<th>Event</th>
<th>Intensive No. of Events</th>
<th>Rate, %/year</th>
<th>Standard No. of Events</th>
<th>Rate, %/year</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>243</td>
<td>1.65</td>
<td>319</td>
<td>2.19</td>
<td>0.75 (0.64, 0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All MI</td>
<td>97</td>
<td>0.65</td>
<td>116</td>
<td>0.78</td>
<td>0.83 (0.64, 1.09)</td>
<td>0.19</td>
</tr>
<tr>
<td>Non-MI ACS</td>
<td>40</td>
<td>0.27</td>
<td>40</td>
<td>0.27</td>
<td>1.00 (0.64, 1.55)</td>
<td>0.99</td>
</tr>
<tr>
<td>All Stroke</td>
<td>62</td>
<td>0.41</td>
<td>70</td>
<td>0.47</td>
<td>0.89 (0.63, 1.25)</td>
<td>0.50</td>
</tr>
<tr>
<td>All HF</td>
<td>62</td>
<td>0.41</td>
<td>100</td>
<td>0.67</td>
<td>0.62 (0.45, 0.84)</td>
<td>0.002</td>
</tr>
<tr>
<td>CVD Death</td>
<td>37</td>
<td>0.25</td>
<td>65</td>
<td>0.43</td>
<td>0.57 (0.38, 0.85)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Primary Outcome Experience in the Six Pre-specified Subgroups of Interest

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.75 (0.64, 0.89)</td>
<td></td>
</tr>
<tr>
<td>No Prior CKD</td>
<td>0.70 (0.56, 0.87)</td>
<td>0.36</td>
</tr>
<tr>
<td>Prior CKD</td>
<td>0.82 (0.63, 1.07)</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 75</td>
<td>0.80 (0.64, 1.00)</td>
<td>0.32</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>0.67 (0.51, 0.86)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.84 (0.62, 1.14)</td>
<td>0.45</td>
</tr>
<tr>
<td>Male</td>
<td>0.72 (0.59, 0.88)</td>
<td></td>
</tr>
<tr>
<td>African–American</td>
<td>0.77 (0.55, 1.06)</td>
<td>0.83</td>
</tr>
<tr>
<td>Non African–American</td>
<td>0.74 (0.61, 0.90)</td>
<td></td>
</tr>
<tr>
<td>No Prior CVD</td>
<td>0.71 (0.57, 0.90)</td>
<td>0.39</td>
</tr>
<tr>
<td>Prior CVD</td>
<td>0.83 (0.62, 1.09)</td>
<td></td>
</tr>
<tr>
<td>SBP ≤ 132</td>
<td>0.70 (0.51, 0.95)</td>
<td>0.77</td>
</tr>
<tr>
<td>132 &lt; SBP &lt; 145</td>
<td>0.77 (0.57, 1.03)</td>
<td></td>
</tr>
<tr>
<td>SBP ≥ 145</td>
<td>0.83 (0.63, 1.09)</td>
<td></td>
</tr>
</tbody>
</table>

*Treatment by subgroup interaction
*Unadjusted for multiplicity
All-cause Mortality
Cumulative Hazard

Hazard Ratio = 0.73 (95% CI: 0.60 to 0.90)

During Trial (median follow-up = 3.26 years)
Number Needed to Treat (NNT) to Prevent a death = 90

Standard
(210 deaths)

Intensive
(155 deaths)
# All-cause Mortality Experience in the Six Pre-specified Subgroups of Interest

**Figure 4: All-Cause Mortality**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intensive</th>
<th>Standard</th>
<th>HR</th>
<th>Int P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>155/4678 (3.31)</td>
<td>210/4683 (4.48)</td>
<td>0.73 (0.60, 0.90)</td>
<td></td>
</tr>
<tr>
<td>No Prior CKD</td>
<td>85/3348 (2.54)</td>
<td>115/3367 (3.42)</td>
<td>0.75 (0.57, 1.00)</td>
<td>0.76</td>
</tr>
<tr>
<td>Prior CKD</td>
<td>70/1330 (5.26)</td>
<td>95/1316 (7.22)</td>
<td>0.73 (0.53, 1.00)</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 75</td>
<td>82/3361 (2.44)</td>
<td>104/3364 (3.09)</td>
<td>0.77 (0.58, 1.03)</td>
<td>0.58</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>73/1317 (5.54)</td>
<td>106/1319 (8.04)</td>
<td>0.68 (0.50, 0.92)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46/1684 (2.73)</td>
<td>54/1648 (3.28)</td>
<td>0.85 (0.57, 1.26)</td>
<td>0.49</td>
</tr>
<tr>
<td>Male</td>
<td>109/2994 (3.64)</td>
<td>156/3035 (5.14)</td>
<td>0.71 (0.55, 0.91)</td>
<td>*</td>
</tr>
<tr>
<td>African-American</td>
<td>53/1454 (3.65)</td>
<td>55/1493 (3.68)</td>
<td>0.96 (0.65, 1.40)</td>
<td>0.06</td>
</tr>
<tr>
<td>Non African-American</td>
<td>102/3224 (3.16)</td>
<td>155/3190 (4.86)</td>
<td>0.64 (0.50, 0.82)</td>
<td></td>
</tr>
<tr>
<td>No Prior CVD</td>
<td>106/3738 (2.84)</td>
<td>140/3746 (3.74)</td>
<td>0.75 (0.58, 0.96)</td>
<td>0.78</td>
</tr>
<tr>
<td>Prior CVD</td>
<td>49/940 (5.21)</td>
<td>70/937 (7.47)</td>
<td>0.70 (0.48, 1.02)</td>
<td></td>
</tr>
<tr>
<td>SBP ≤ 132</td>
<td>46/1583 (2.91)</td>
<td>64/1553 (4.12)</td>
<td>0.73 (0.49, 1.07)</td>
<td>0.70</td>
</tr>
<tr>
<td>132 &lt; SBP &lt; 145</td>
<td>41/1489 (2.75)</td>
<td>63/1549 (4.07)</td>
<td>0.69 (0.46, 1.03)</td>
<td></td>
</tr>
<tr>
<td>SBP ≥ 145</td>
<td>68/1606 (4.23)</td>
<td>83/1581 (5.25)</td>
<td>0.81 (0.59, 1.13)</td>
<td></td>
</tr>
</tbody>
</table>

*p=0.34, after Hommel adjustment for multiple comparisons*
## Renal Disease Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Standard</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants with CKD at Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary CKD outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50% reduction in eGFR*</td>
<td>14 0.33</td>
<td>15 0.36</td>
<td>0.89 (0.42, 1.87)</td>
<td>0.76</td>
</tr>
<tr>
<td>Dialysis</td>
<td>10 0.23</td>
<td>11 0.26</td>
<td>0.87 (0.36, 2.07)</td>
<td>0.75</td>
</tr>
<tr>
<td>Kidney transplant</td>
<td>0 -</td>
<td>0 -</td>
<td>-</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Secondary CKD Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident albuminuria**</td>
<td>49 3.02</td>
<td>59 3.90</td>
<td>0.72 (0.48, 1.07)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

| **Participants without CKD at Baseline** |           |          |             |     |
| **Secondary CKD outcomes** |           |          |             |     |
| ≥30% reduction in eGFR* | 127 1.21  | 37 0.35  | 3.48 (2.44, 5.10) | <0.0001 |
| Incident albuminuria** | 110 2.00  | 135 2.41 | 0.81 (0.63, 1.04) | 0.10 |

*Confirmed on a second occasion ≥90 days apart  **Doubling of urinary albumin/creatinine ratio from <10 to >10 mg/g
### Serious Adverse Events* (SAE) During Follow-up

<table>
<thead>
<tr>
<th>All SAE reports</th>
<th>Number (%) of Participants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Standard</td>
</tr>
<tr>
<td></td>
<td>1793 (38.3)</td>
<td>1736 (37.1)</td>
</tr>
</tbody>
</table>

### SAEs associated with Specific Conditions of Interest

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intensive</th>
<th>Standard</th>
<th>HR (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>110 (2.4)</td>
<td>66 (1.4)</td>
<td>1.67 (0.001)</td>
</tr>
<tr>
<td>Syncope</td>
<td>107 (2.3)</td>
<td>80 (1.7)</td>
<td>1.33 (0.05)</td>
</tr>
<tr>
<td>Injurious fall</td>
<td>105 (2.2)</td>
<td>110 (2.3)</td>
<td>0.95 (0.71)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>87 (1.9)</td>
<td>73 (1.6)</td>
<td>1.19 (0.28)</td>
</tr>
<tr>
<td>Electrolyte abnormality</td>
<td>144 (3.1)</td>
<td>107 (2.3)</td>
<td>1.35 (0.020)</td>
</tr>
<tr>
<td>Acute kidney injury or acute renal failure</td>
<td>193 (4.1)</td>
<td>117 (2.5)</td>
<td>1.66 (&lt;0.001)</td>
</tr>
</tbody>
</table>

*Fatal or life threatening event, resulting in significant or persistent disability, requiring or prolonging hospitalization, or judged important medical event.
<table>
<thead>
<tr>
<th>Laboratory Measures</th>
<th>Number (%) of Participants</th>
<th>HR (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium &lt;130 mmol/L</td>
<td>180 (3.9)</td>
<td>1.76 (&lt;0.001)</td>
</tr>
<tr>
<td>Potassium &lt;3.0 mmol/L</td>
<td>114 (2.5)</td>
<td>1.50 (0.006)</td>
</tr>
<tr>
<td>Potassium &gt;5.5 mmol/l</td>
<td>176 (3.8)</td>
<td>1.00 (0.97)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Number (%) of Participants</th>
<th>HR (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic hypotension</td>
<td>777 (16.6)</td>
<td>0.88 (0.013)</td>
</tr>
<tr>
<td>Orthostatic hypotension with dizziness</td>
<td>62 (1.3)</td>
<td>0.85 (0.35)</td>
</tr>
</tbody>
</table>
• SPRINT examined effects of more intensive antihypertensive therapy than currently recommended
• Participants were US adults ≥50 years with hypertension and additional risk for CVD
• Rapid and sustained difference in SBP achieved between the two treatment arms
• Trial stopped early, due to benefit, after median follow-up of 3.26 years
• Incidence of primary outcome (composite of CVD events) 25% lower in Intensive compared to Standard Group and all-cause mortality reduced by 27%.
• Treatment effect similar in all six pre-specified groups of interest.
• The “number needed to treat” to prevent primary outcome event or death 61 and 90, respectively
Summary and Conclusions

- In participants with CKD at baseline, no differences in renal outcomes

- In participants without CKD at baseline, incidence of eGFR reduction ≥ 30% more common in Intensive Group

- No overall difference in serious adverse events (SAEs) between treatment groups

- SAEs associated with hypotension, syncope, electrolyte abnormalities, and hospital discharge reports of acute kidney injury or acute renal failure more common in Intensive Group

- Overall, benefits of more intensive BP lowering exceeded the potential for harm
In Perspective

- Estimated that 16 million Americans have clinical characteristics similar to the enrolled population in SPRINT and could benefit from lower BP goals
- Includes the message that there is no conservative strategy in the elderly and challenges prior guidelines (in fact, those > 75 yrs had greater benefit than younger subjects)
- As opposed to ACCORD, study was well powered
- Broad representation of women, African-Americans, elderly, CKD and those with CV disease
- Stresses thinking about CV risk as a criterion for therapy initiation in patients who may have SBP > 120 mmHg
Other Recent Evidence

• Largest meta-analysis of 123 large-scale trials of BP lowering in 613,815 patients:
  – 10 mmHg reduction in SBP reduced the risk of major CVD events by 20%
    • Coronary heart disease by 17%
    • Stroke by 27%
    • Heart failure by 28%
    • All-cause mortality by 13%
  – Similar to SPRINT, benefit seen in those with lower baseline SBP but with elevated CV risk

Ettehad et al. Lancet March 2016
In Perspective: Some Issues with SPRINT

• Reduced development of heart failure largely drove the overall CV benefit
  – Subjective outcome measure and investigators were unblinded
  – Greater use of diuretics in treatment arm which may have accounted for this

• Unexplained that intensive treatment did not lower the risk of stroke, myocardial infarction or acute coronary syndrome

• Intensive BP control requires at least one additional medication:
  – Risk of orthostatic hypotension, AKI and electrolyte abnormalities were higher in intensive treatment group- may effect long-term adherence outside of a clinical trial environment

• In the trial, 90% of patients were treated at baseline and thus initiation guidelines are unclear (> 140 mmHg in the untreated patient?)

• Excluded diabetic patients where in the ACCORD trial there was no benefit of more intensive BP control- ? reasons
Design Issues

• The SBP groups had widely different BP achieved:
  – No information if there is a gradient and perhaps a more tolerable goal with fewer adverse effects
  – Will be investigated in the Optimal Blood Pressure and Cholesterol Targets for Preventing Recurrent Stroke in Hypertensives (ESH-CHL-SHOT) with three different BP goals

• Since the trial was terminated early, the magnitude of the benefit may be overestimated
Blood Pressure Measurement in SPRINT

• Much has been made that the BP measurement in SPRINT was different from clinical practice:
  – 3 automated measurements after 5 minutes of rest
  – Largely unattended measurements

• Do we have to adopt SPRINT BP measurement techniques to see the estimated benefit of intensive BP treatment?
Compared to ACCORD

- Larger trial with adequate power to demonstrate outcomes
- Higher risk overall
- ACCORD did show 12% reduction in risk in primary outcome and confidence intervals suggested possibility of benefits similar to that seen in SPRINT
- ACCORD may have been confounded by 2 x 2 design with both BP and glycemic control arms with an interaction between tight glycemic control and BP effect on CV outcomes
- A reanalysis of ACCORD did demonstrate that intensive BP treatment alone with usual glucose control compared with standard treatment improved CV outcomes
### SPRINT v. ACCORD

<table>
<thead>
<tr>
<th></th>
<th>SPRINT</th>
<th>ACCORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort Size</td>
<td>9361</td>
<td>4733</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>68</td>
<td>62</td>
</tr>
<tr>
<td>Design</td>
<td>Randomized controlled</td>
<td>Randomized controlled 2 x 2 study</td>
</tr>
<tr>
<td>Intensive (n) &lt; 120 mmHg</td>
<td>4678</td>
<td>2362</td>
</tr>
<tr>
<td>Standard (n) &lt; 140 mmHg</td>
<td>4683</td>
<td>2371</td>
</tr>
<tr>
<td>Mean SBP (intensive) at 1 yr</td>
<td>121.4</td>
<td>119.3</td>
</tr>
<tr>
<td>Mean SBP (standard) at 1 yr</td>
<td>136.2</td>
<td>133.5</td>
</tr>
<tr>
<td>HR for Primary Outcome</td>
<td>0.75 (0.64-0.89) p&lt;0.001</td>
<td>0.88 (0.73-1.06) p=0.2</td>
</tr>
<tr>
<td>All cause mortality (intensive v. standard)</td>
<td>0.73 (0.60-0.90) p =0.003</td>
<td>1.07 (0.85-1.35) p =0.55</td>
</tr>
<tr>
<td>CV mortality (intensive v. standard)</td>
<td>0.57 (0.38-0.85) p = 0.005</td>
<td>1.06 (0.74-1.52) p =0.74</td>
</tr>
</tbody>
</table>
Impact on Chronic Kidney Disease

• Failure of lower BP to slow CKD progression or to prevent CKD
• In fact, intensive group had a higher rate of eGFR reduction
• Consistent with other trials (albeit small data base)
  – Similar rates of CKD progression at mean 125/75 mmHg vs. 140/90 mmHg
• However, one of the few interventions that has been shown to reduce CV mortality in the CKD population is better BP control
Specific Populations: Elderly

- Prior studies such as HYVET, STOP, SHEP had also shown significant mortality and CV outcome benefit with SBP lowering (< 150 mmHg) thus guidelines focused on this higher SBP goal
- SPRINT: In the population age > 75 years:
  - Benefits of intensive therapy were greater (34% in primary outcome)
  - Number needed to treat over 3.26 years to prevent one event was 28 in the elderly group
  - The pattern of adverse events in this group was similar to the entire cohort

In those patients age > 75 mmHg, aggressive lowering of BP should be considered but carefully weighed against the individual risks in the patient
Specific Populations: CKD Patients

• Affects 8-16% of the population with the major cause of death being CV events and 86% of patients have hypertension

• BP goals for this population had been controversial and after 2013 major guidelines had relaxed BP goals towards higher levels:
  – European Society of Hypertension: <140/90 mmHg
  – JNC 8 (2014): nondiabetic patients: <150/90 mmHg
  – KDIGO: <140/90 mmHg and <130/80 mmHg with > 30 mg/d albuminuria

Key clinical question is whether same BP goal arrests CKD progression and protection from CV events.
Relationship Between Mortality and BP in CKD

- Relationship is more complex in CKD patients
- May reflect arterial stiffness and hazards of lower BP if BP falls below autoregulatory threshold
- Age is a modifier of this relationship:
  - Higher SBP was associated with higher CV risk in all ages but magnitude is lower with advanced age

BP and Renal Outcomes in CKD

• In general, data has supported benefit of SBP < 140 mmHg for the slowing of GFR loss and progression to ESRD

• Levels of baseline proteinuria modify this relationship such that those with > 1 gm/d of proteinuria benefit from lowering to SBP 110-129 mmHg

• However, lower BP goals seem to be associated with higher rates of progression
Specific Populations: CKD Patients

- SPRINT enrolled 2646 participants with baseline CKD (eGFR 20-59 ml/min)
  - Primary outcome was reduced with intensive treatment (HR 0.82, CI 0.63-1.07)
  - Less pronounced reduction of CV events in the CKD cohort
Specific Populations: Diabetic Patients

- Area remains controversial with little data to support lower BP targets in this group
- ACCORD (Action to Control Cardiovascular Risk in Diabetes)
  - Stricter SBP goal < 120 mmHg reduced stroke rate but NOT other CV events compared to 140 mmHg
- Ettehad et al meta-analysis:
  - The relative risk reduction for diabetics with lower SBP is lower than in those with diabetes
- Another meta-analysis of 73,738 participants (majority diabetic):
  - Treating those with baseline SBP > 140 mmHg reduced mortality and CV events
  - Treating those with baseline SBP < 140 mmHg did not demonstrate benefit

Mattias et al BMJ 2016
Issues of BP Measurement

• SPRINT: unobserved, automated device used for 3 readings after 5 minutes of rest
• Mean clinic BP in the intensive group was 7 mmHg lower compared with the daytime ambulatory SBP
• In usual practice, clinic BP is taken manually in less than ideal circumstances leading to an overestimation of BP
• Such overestimation of BP may lead to overtreatment of hypertension increasing the risk of adverse events if the SPRINT target was used
The Issue of Baseline CV Risk

• SPRINT demonstrated benefit in a high CV risk group
• Supports the use of CV risk stratification in deciding upon treatment and goals
• Those with the highest CV risk derive the greatest relative benefit
  – Most true for older patients
  – Data in patients < 50 yrs is less robust
What About Drug Selection?

• In SPRINT, most patients taking ACEi/ARBs and diuretics and trial did not specifically address whether one drug choice was superior to another in terms of outcomes

• Recent meta-analysis:
  – β blockers were inferior to other drugs for the prevention of major cardiovascular disease events, stroke, and renal failure.
  – Calcium channel blockers were superior to other drugs for the prevention of stroke.
  – For the prevention of heart failure, calcium channel blockers were inferior and diuretics were superior to other drug classes.
Recommendations

• In those patients who can safely tolerate lower BP goals, there is now good rationale to target these goals
  – Includes patients > 75 years
  – Same inclusion criteria as the trial

• Concerns in patients
  – Arterial stiffness (low diastolic BPs)
  – Frail elderly patients
### Balance

<table>
<thead>
<tr>
<th><strong>Potential Benefits of Lower BP Goal</strong></th>
<th><strong>Potential Risk of Lower BP Goal</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in all-cause mortality</td>
<td>Reduction in end-organ perfusion</td>
</tr>
<tr>
<td></td>
<td>- Renal function decline and AKI</td>
</tr>
<tr>
<td></td>
<td>- Cerebral perfusion</td>
</tr>
<tr>
<td>Reduction in CV events and mortality</td>
<td>Reduction in diastolic BP:</td>
</tr>
<tr>
<td></td>
<td>- Myocardial hypoperfusion and rise in CV mortality</td>
</tr>
<tr>
<td>?Reduction in CKD progression and development of ESRD (CKD patients)</td>
<td>Patient burden, costs and adverse events</td>
</tr>
</tbody>
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