Management of hypertension in the long run:

more than just SPRINTing or HOPEing

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OBJECTIVES

• At the completion of this session participants should be able to critically appraise and define how the SPRINT and HOPE-3 trial results will be incorporated into practice.

• As outlined in the 2016 CHEP recommendations the SPRINT trial results will change my management of hypertensive patients.
Presenter Disclosure

- Faculty: Ross Feldman
- Relationships with commercial interests:
  - Grants/Research Support: **Bayer**
  - Speakers Bureau/Honoraria: **Bayer, Servier, Valeant**
  - Consulting Fees: **Servier, Valeant**
  - Other: **NA**
Mitigating Potential Bias

• The content is based on Hypertension Canada’s CHEP recommendations
September 24, 2015

Mr. PS is a pleasant 82 year old gentleman that you have been following for years. He has had some progressive symptoms associated with a peripheral neuropathy but gets along well on a cane (mostly).

You have been following his blood pressure lately. Office and home BPs have been persistently in the 155-160 mmHg range despite some lifestyle modifications.

His BP that day was 158/82 which dropped 5 mmHg when he got up.
What should you have done about his blood pressure?

1. Tell him to stop taking his blood pressure (if it ain’t broke don’t fix it).
2. Tell him that if it rises much further he will need to start on drug therapy
3. Start him on a low dose diuretic
4. Start him on 2-drug therapy
Today

Mr. PS comes back for a regular followup visit. In the interim he has been well...he is using his walker a little more.

His blood pressure has been the same...maybe a little lower with home BPs in the 150-155 range. He has been persistent in his lifestyle modifications- reducing his intake of processed foods and alcohol.

Today his BP is 153/78 with not much change when he stands up.
Now… what should you do about his blood pressure?

1. Tell him to stop taking his blood pressure (if it ain’t broke don’t fix it).
2. Tell him that if it rises much further he will need to start on drug therapy
3. Start him on a low dose diuretic
4. Start him on 2-drug therapy
Risk of CHD mortality with increasing BP (MRFIT)

- **Systolic**
- **Diastolic**

### Adjusted Relative Risk

<table>
<thead>
<tr>
<th>Decile</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;112</td>
<td>&lt;71</td>
</tr>
<tr>
<td>2</td>
<td>112-</td>
<td>71-</td>
</tr>
<tr>
<td>3</td>
<td>118-</td>
<td>76-</td>
</tr>
<tr>
<td>4</td>
<td>121-</td>
<td>79-</td>
</tr>
<tr>
<td>5</td>
<td>125-</td>
<td>81-</td>
</tr>
<tr>
<td>6</td>
<td>129-</td>
<td>84-</td>
</tr>
<tr>
<td>7</td>
<td>132-</td>
<td>86-</td>
</tr>
<tr>
<td>8</td>
<td>137-</td>
<td>89-</td>
</tr>
<tr>
<td>9</td>
<td>142-</td>
<td>92-</td>
</tr>
<tr>
<td>10</td>
<td>≥151</td>
<td>≥98</td>
</tr>
</tbody>
</table>

The relative risk reduction with increasing SBP reduction remains linear (mostly)

Benefit of BP lowering in the “average” hypertensive (i.e., middle aged male)

Number-needed-to-treat (NNT$_{10\text{ yr}}$) to prevent a CV event/death or a death from all causes by BP lowering

<table>
<thead>
<tr>
<th></th>
<th>Stage 1</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No other risk factors</td>
<td>60</td>
<td>23</td>
</tr>
<tr>
<td>(beyond age and male gender)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 other risk factor</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>+ CVD or TOD</td>
<td>12</td>
<td>9</td>
</tr>
</tbody>
</table>

TOD=target organ damage

Ogden et al. *Hypertension* 2000;35:539-43
**Last year’s CHEP threshold values for initiation of pharmacological treatment**

<table>
<thead>
<tr>
<th>Population</th>
<th>SBP ≥</th>
<th>DBP ≥</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>130</td>
<td>80</td>
</tr>
<tr>
<td>High risk (TOD or CV risk factors)</td>
<td>140</td>
<td>90</td>
</tr>
<tr>
<td>Low risk (no TOD or CV risk factors)</td>
<td>160</td>
<td>100</td>
</tr>
<tr>
<td>Very elderly* (≥80 yrs.)</td>
<td>160</td>
<td>NA</td>
</tr>
</tbody>
</table>

*TOD = target organ damage

*This higher treatment target for the very elderly reflects current evidence and heightened concerns of precipitating adverse effects, particularly in frail patients. Decisions regarding initiating and intensifying pharmacotherapy in the very elderly should be based upon an individualized risk-benefit analysis.*
**Last year’s CHEP-recommended treatment targets**

Treatment consists of health behaviour ± pharmacological management

<table>
<thead>
<tr>
<th>Population</th>
<th>SBP &lt;</th>
<th>DBP &lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>130</td>
<td>80</td>
</tr>
<tr>
<td>All others &lt; 80 yrs. (including CKD)</td>
<td>140</td>
<td>90</td>
</tr>
<tr>
<td>Very elderly (≥ 80 yrs.)</td>
<td>150</td>
<td>NA</td>
</tr>
</tbody>
</table>

In patients with coronary artery disease be cautious when lowering blood pressure if diastolic blood pressures are < 60mmHg
**This Year’s CHEP Threshold Values for Initiation of Pharmacological Treatment**

<table>
<thead>
<tr>
<th>Population</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk (SPRINT population)</td>
<td>≥130</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥130</td>
<td>≥80</td>
</tr>
<tr>
<td>Moderate-to-high risk (TOD or CV risk factors)*</td>
<td>≥140</td>
<td>≥90</td>
</tr>
<tr>
<td>Low risk (no TOD or CV risk factors)</td>
<td>≥160</td>
<td>≥100</td>
</tr>
</tbody>
</table>

**TOD =** target organ damage

*AOBP threshold ≥135/85
Treatment consists of health behaviour ± pharmacological management

<table>
<thead>
<tr>
<th>Population</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>≤120</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&lt; 130</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>All others*</td>
<td>&lt; 140</td>
<td>&lt; 90</td>
</tr>
</tbody>
</table>

* Target BP with AOBP < 135/85
For high-risk patients, aged ≥ 50 years, with systolic BP levels ≥130 mm Hg, intensive management to target a systolic BP ≤120 mm Hg should be considered.

Intensive management should be guided by automated office BP measurements.

Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups.
New Thresholds/Targets for the high risk patient
Post-SPRINT: who does this apply to??

- Clinical or sub-clinical cardiovascular disease
  OR
- Chronic kidney disease (non-diabetic nephropathy, proteinuria <1 g/d, *estimated glomerular filtration rate 20-59 mL/min/1.73m²)
  OR
- †Estimated 10-year global cardiovascular risk ≥15%
  OR
- Age ≥ 75 years

Patients with one or more clinical indications should consent to intensive management.

* Four variable MDRD equation
† Framingham Risk Score, D'Agastino, Circulation 2008
New Thresholds/Targets for the high risk patient post-SPRINT: who does this NOT apply to??

Limited or No Evidence:
• Heart failure (EF <35%) or recent MI (within last 3 months)
• Indication for, but not currently receiving a beta-blocker
• Institutionalized elderly

Inconclusive Evidence:
• Diabetes mellitus
• Prior stroke
• eGFR < 20 ml/min/1.73m2

Contraindications:
• Patient unwilling or unable to adhere to multiple medications
• Standing SBP <110 mmHg
• Inability to measure SBP accurately
• Known secondary cause(s) of hypertension
SPRINT: SBPs Achieved

Average no. of medications
Intensive care: 2.8
Standard care: 1.8
SPRINT Primary Outcome

NNT=61

Hazard ratio with intensive treatment,
0.75 (95% CI, 0.64–0.89)

Cumulative Hazard

Standard treatment

Intensive treatment

No. at Risk

Standard treatment

Intensive treatment

Years

SPRINT: Primary Cardiovascular Disease Outcome by Baseline Frailty Status

Tinted regions indicate 95% confidence intervals; FI, 37-item frailty index

HR, 0.47 (95% CI, 0.13-1.39); Cox regression $P = .20$

No. at risk
Type of treatment
Standard 190
Intensive 159

0 1 2 3
Years

Cumulative Hazard

HR, 0.63 (95% CI, 0.43-0.91); Cox regression $P = .01$

Less fit (FI >0.10 to ≤0.21)

No. at risk
Type of treatment
Standard 186
Intensive 151

0 1 2
Years

Cumulative Hazard

HR, 0.68 (95% CI, 0.45-1.01); Cox regression $P = .06$

Frail (FI >0.21)

No. at risk
Type of treatment
Standard 745
Intensive 711

0 1 2 3 4 5
Years

Cumulative Hazard

No. at risk
Type of treatment
Standard 375
Intensive 440
Management of hypertension in the long run: *post-SPRINT*

- Hypertension-related complications increase from SBPs in the 120 mmHg range.

- The benefits of antihypertensive treatment increase with increasing overall CV risk.

- SPRINT has finally provided the proof-of-principle that there is a significant CV benefit of lower BP targets for those at highest risk.
BACKGROUND: Antihypertensive therapy reduces the risk of cardiovascular events among high-risk persons and among those with a systolic blood pressure of 160 mm Hg or higher, but its role in persons at intermediate risk and with lower blood pressure is unclear.

METHODS: In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants at intermediate risk who did not have cardiovascular disease to receive either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; the second coprimary outcome additionally included resuscitated cardiac arrest, heart failure, and revascularization. The median follow-up was 5.6 years.

RESULTS: The mean blood pressure of the participants at baseline was 138.1/81.9 mm Hg; the decrease in blood pressure was 6.0/3.0 mm Hg greater in the active-treatment group than in the placebo group. The first coprimary outcome occurred in 260 participants (4.1%) in the active-treatment group and in 279 (4.4%) in the placebo group (hazard ratio, 0.93; 95% confidence interval [CI], 0.79 to 1.10; P=0.40); the second coprimary outcome occurred in 312 participants (4.9%) and 328 participants (5.2%), respectively (hazard ratio, 0.95; 95% CI, 0.81 to 1.11; P=0.51).

CONCLUSIONS: Therapy with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day was not associated with a lower rate of major cardiovascular events than placebo among persons at intermediate risk who did not have cardiovascular disease.
BP lowering NOT effective in reducing risk (too much to HOPE for?)

- Combo: 28%
- Rosuva Only: 26%
- Cand + HCTZ Only: 6%
“Our findings contradict the lower is better hypothesis that has been derived from epidemiologic studies, and our findings support the concept that a J-curve phenomenon exists for major cardiovascular events, other than for stroke, in this population.”
LOST
CONFUSED
UNSURE
UNCLEAR
PERPLEXED
DISORIENTED
BEWILDERED
At this point....

1. Are you a SPRINTer?
2. Are you a HOPEr?
It’s a Fan!

It’s a Spear!

It’s a Wall!

It’s a Rope!

It’s a Snake!

It’s a Tree!
SPRINT vs HOPE-3: the same elephant?

SPRINT
- N= 9361
- FU= 3.3 yrs
- 10 yr risk= 21% (FRS 17)
- BP change= 19/8 mmHg
- Hazard Ratio= 0.75

HOPE-3
- N= 12,705
- FU= 5.6 yrs
- 10 yr risk= 8% (InterheartRS 14.5)
- BP change= 6/3 mmHg
- Hazard Ratio 0.93 (NS)
or is HOPE-3 just a reprise of ASCOT a decade later?
Conclusions

• The risk of hypertension-related CV complications rise at SBP >120 mmHg.
• The benefits of antihypertensive therapy are more dependent on global cardiovascular risk than extent of BP rise
• Based on SPRINT, for those at greatest risk of CV complications the threshold and target BPs should be 130 and 120 mmHg (respectively).
• For this at intermediate risk of CV complications HOPE-3 has re-affirmed that 140 mmHg remains a reasonable target/threshold

….and thank goodness for both elephants and visually challenged medical commentators