Goals and targets in hypertension: the SPRINT
(systolic blood pressure intervention trial)

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Objectives

1) Three subtly-different hypertensive patients
2) Systolic blood pressure intervention trial:
   • Patients, treatment, comparator, outcomes
   • Expected features of study outcomes
   • Unusual features in outcomes (?internal validity)
   • External validity – how applicable in SG?
3) Added insights from Williamson et al.’s outcomes comparison in ambulatory persons >75y (online JAMA 19.5.2016)
4) Consider first principles from CVS physiology
5) What new points might apply to SG patients ≥ 60y?
   What’s applicable to our patients ≥ 75y?
1) Zones of Doubt for Your Resolution

Three cases with different features, different trajectories across time, and hence different key-determinants of CV disease outcomes
Case A: A 66 y.o. non-smoking woman has a BMI of 25 and a 24-hour ambulatory blood pressure (BP) mean of 162/88 mmHg. No history of TIA/stroke or acute coronary syndrome. Normal physical examination, except left ventricular heave. Her glycated haemoglobin is 58 mmol/mol (6.5%); serum creatinine 101 µmol/l, with normal electrolytes. Her serum LDL-cholesterol is 3.5 mmol/l; LV ejection fraction 52%.
**Case B:** A 77 y.o. diabetic man, former-smoker, has BMI of 28, and average home BP of **158/91 mmHg**. History includes transient ischemic attack when 74. No clinical evidence of carotid insufficiency; LVEF 46%. He takes aspirin 100mg daily, furosemide and metoprolol for NYHA-class-1 heart failure; perindopril and felodipine; acarbose, metformin & sitagliptin. HbA$_{1c}$ 61 mmol/mol (7.6%), serum Na$^+$ 138, K$^+$ 3.7 mmol/l, urea 6.9 mmol/l, creatinine 122 µmol/l, eGFR 50 ml/min. Urinary ACR 34 mg/mmol.
Case C: A 79 y.o. non-diabetic man, former-smoker, has BMI of 26, and home BP mean of 168/65 mmHg. Supine BP 171/64, upright 154/68 mmHg. History of TICA aged 74, and possible transient global amnesia. He has bilateral carotid bruits. Stable angina pectoris for 8 years; LVEF 43%; PCI declined. He takes aspirin + clopidogrel; for NYHA-class-2 heart failure he takes furosemide, nebivolol and eplerenone; and rosuvastatin for dyslipidemia. Antihypertensives: valsartan, amlodipine, and terazosin. HbA₁c 48 mmol/mol (6.2%), serum Na⁺ 138, K⁺ 4.9 mmol/l, urea 7.4 mmol/l, creatinine 119 µmol/l, eGFR 53 ml/min; urinary ACR 24 mg/mmol.
For Cases A, B and C:

- What is the global cardiovascular risk?
- What will this CV risk be in the expected time span?
- What physiological factors govern CV trajectory?
  - How best to optimize risk reduction vs QoL, i.e. what BP targets are apt?
- How might SPRINT & ‘SPRINT -75’ help us to answer the above questions?
2) From SPRINT:

- In 9361 ambulatory non-diabetic hypertensive persons without significant CKD, treating to systolic BP <120 mmHg protects vs nonfatal AMI, ACS, death from other CV causes, compared with SBP <140.

- M:F = 72:28; 58% non-Hispanic white; 11% Hispanic; 30% black
  - 4678 intensive Rx, 4683 standard Rx.
  - Achieved BP 121.4 mmHg vs 136.2

- Primary outcome was composite of AMI, other ACS types, stroke, heart-failure & death from other CVS causes.
  - Secondary outcome was all-cause death.
2) From SPRINT:

- Primary-endpoint rate at 3.26 years was 1.65% pa (intensive Rx) vs 2.19% pa (standard Rx).

- Primary outcome: HR for intensive Rx = 0.75 (95% CI, 0.64-0.89) (P<0.001).
  - Secondary outcome: HR for intensive Rx = 0.73 (0.60-0.90) (P<0.003).

- Trial stopped early – we don’t know if outcomes might have altered at 5 years or later.
2) From SPRINT:

- Designed to raise recruitment of older adults, BUT did not stratify randomization by age.
  - Some older people in nursing-homes excluded.
  - Subgroup of CKD patients too small to interpret properly.

- Over 90% of patients already taking 2 or more anti-HT drugs, so the results do not support starting Rx at BP <140/90.
2) From SPRINT:

- Most of the composite CVS benefit came from reduction in heart-failure event rate, & fewer deaths from other CVS causes; BUT no protection from fatal heart-failure – atypical outcome

- Investigators were NOT blinded to drug treatments

- Greater diuretic use in intensive group: this could have masked heart failure (HF) symptoms instead of preventing HF; misclassification could explain lack of HF prevention.
2) From SPRINT:

- No protection vs stroke: a peculiar outcome, because almost every sufficiently-powered antihypertensive treatment trial has shown significant stroke prevention, regardless of co-morbid diabetes

- Comparison with ACCORD trial 2010 → Diabetic hypertensive patients treated to systolic BP ≤120 mmHg had significant & similar serious adverse effects as SPRINT

- Which suggests that adverse effects are consistent
3) From ‘SPRINT-75’

- In 2636 ambulatory non-diabetic hypertensive persons without significant CKD, mean age 79.9 (m:f = 62:38) treating for median 3.1 years to systolic BP <120 mmHg vs SBP <140, protects vs *composite outcome* of nonfatal AMI, ACS, nonfatal stroke, nonfatal heart-failure + death from other CV causes.

- Intensive Rx: composite outcome hazard ratio 0.66 (95%CI, 0.51-0.85);

- All-cause death HR 0.67 (95%CI, 0.49-0.91).

- No protection from fatal AMI, stroke, or heart-failure (as with SPRINT).
3) From ‘SPRINT-75’

- Rate of serious adverse events 48.4% vs 48.3%
- Absolute rate of hypotension 2.4% vs 1.4% (HR 1.71)
  - Syncope 3.0% vs 2.4% (HR 1.23)
  - Injurious falls 4.9% vs 5.5% (HR 0.91)
- Absolute rate of AKI 5.5% vs 4.0% (HR 1.41)

ALL the 95% CIs crossed 1.0, but tendency was consistent
4) Old Question about Lower BP Limit to CV Event Prevention

At higher BP levels CV disease is more frequent and more severe; thus, usually, larger benefits accrue to older persons & more severe hypertension

‘But is there a lower BP limit to the preventive effect on cardiovascular disease & death by antihypertensive treatment?’
4) Risk Information from Big Datasets

- Actuarial data from many populations \((n = 10^8)\) of many ethnic origins & dietary patterns show: the longest survivors among non-hypertensive people have the lowest quintile of BP.

- Meta-analyses of RCTs of treated hypertensive patients: similar trend in persons aged under 76 years \((\text{BPLTTTC } \textit{Lancet} 2000;355:1955-64)\).
4) RCT Evidence for No Lower BP Limit to CV Protective Benefit

Apparently ‘no lower BP limit’ to the preventive effect on cardiovascular death:

**Example 1**

BP \( \approx 115/75 \) mmHg


**Example 2**

Diastolic BP < 80 mmHg

4) No Lower BP Limit to CVS Protection?

Example 3
Average BP $\approx 110/70$ mmHg

Meta-analysis of 147 RCTs, 958,000 persons, suggested that lowering BP to 110/70 mmHg confers benefit in preventing CVS morbidity & mortality …including CV events in heart-failure and recent AMI patients.


HOWEVER:
Systolic & diastolic blood pressure across time

Men

Systolic BP

Diastolic BP

Age (years)

BP (mm Hg)

20 40 60 ≥ 80

Systolic & diastolic blood pressure across time

180 mmHg

70 mmHg
Pressure wave reflection

1. Each cardiac contraction produces an outgoing arterial wave, which is reflected backwards on reaching the periphery.

2. The reflected wave merges with the outgoing arterial wave of the next cardiac contraction, resulting in a summated arterial wave.
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Stiff aorta

Normal

![Graphs showing BP (mm Hg) over time with labeled waves: Outgoing wave, Reflected wave, Summated wave.]

Outgoing wave

Reflected wave

BP (mm Hg)

Time

Systole

Diastole

SBP

DBP
4) CVS physiological limits pertain

- With ageing the systolic BP rises steadily, while the diastolic BP, after peaking at about 55 years, declines to ~70 mmHg at 80 years.

- At 60-95 years, isolated systolic HT affects 55% of patients, limiting the safe reduction in BP to systolic <120 mmHg.

  - MAP = CO x SVR
    (normal 65-110 mmHg)

  - Since mean arterial pressure, MAP = DBP + PP/3, with ageing: as DBP falls and SBP rises, the PP rises.

    - Intensive BP reduction lowers the PP;
      While CO is stable, SVR falls → MAP falls to <60 mmHg.

- Intensive BP control can impair coronary-artery flow during diastole.
5) KEY LEARNING POINTS

From SPRINT + ‘SPRINT-75’, with help from human CVS physiology
5) Main findings from SPRINT & SPRINT-75

- In ambulatory non-diabetic hypertensive persons aged 60-75+ years, without significant CKD, BP lowering for median 3.2 years to systolic BP <120 mmHg vs SBP <140, protects vs AMI, ACS, death from other CV causes

- Intensive Rx: composite outcome hazard ratio 0.66; all-cause death HR 0.67.

- Rate of serious adverse events 48.4% vs 48.3%
- Absolute rate hypotension 2.4% vs 1.4% (HR1.71)
  - Syncope 3.0% vs 2.4%
  - Injurious falls 4.9% vs 5.5%
  - Absolute rate AKI 5.5% vs 4.0%

ALL the 95% CIs crossed 1.0, but ?underestimates
5) From human CVS physiology:

- Structural changes in the heart and arterioles are reversible only within narrow zones, and only before atherosclerosis & fibrotic stiffness (compliance-loss) are advanced.

- Limits are crucial in the ‘operating efficacy’ of the Frank-Starling mechanism for the LV, relating cardiac-output (CO) to systemic vascular resistance (SVR) and venous return.

- Since coronary artery filling occurs during diastole, intra-aortic diastolic pressure cannot fall below certain levels without compromise to myocardial function and CVS outcomes.

- Whereas autoregulation of intracerebral blood flow protects the brain to an extent from systemic hypotension, the extracranial arterial BP does not reliably guide treatment.
5) From human CVS physiology:

- Beyond individual limits of cardiac compensation, the fall in mean arterial pressure, MAP (representing perfusion pressure in pulsatile flow), will affect vital-organ blood supply.

- At MAP < 65 mmHg, corresponding to aortic diastolic pressure below ~ 40 to 55 mmHg, coronary artery filling will decrease, thus affecting myocardial function and CVS outcomes.

- When MAP in the carotid and vertebral arteries falls < 60–65 mmHg, cerebral blood flow can be affected (few human studies, no RCT outcomes with blood-flow data)
5) NEW Mx POINTS TO CONSIDER

- Together, the two studies suggest that in fit, ambulatory, non-diabetic non-CKD patients aged 60 to 75+ years, lowering the BP towards systolic 120 mmHg might confer significant protection vs CV outcomes such as nonfatal AMI, ACS types, nonfatal stroke, and nonfatal heart failure.

- Such benefits accrue with tolerable side effects, even in those aged over 75 (but more robust data needed)

- Robust double-blind RCTs lasting beyond 3 years are needed to increase confidence in these results.

- In carefully-selected, ambulant patients with medium-to-low global CV risk, we can aim stepwise at systolic 130, then 125, towards 120 mmHg.
Case A: A 66 y.o. non-smoking woman has a BMI of 25 and a 24h ambulatory blood pressure (BP) mean of 162/88 mmHg. No history of TIA/stroke or acute coronary syndrome. Normal physical examination, except left ventricular heave. Her glycated haemoglobin is 58 mmol/mol (6.5%); serum creatinine 101 µmol/l, with normal electrolytes. Her serum LDL-cholesterol is 3.5 mmol/l; LV ejection fraction 52%. Apart from lifestyle change, you would apply the following drugs, and cautiously pursue the target BP (mmHg):

A. diltiazem + labetalol: target 150
B. losartan + ramipril: target 140/90
C. atenolol + candesartan: target 135/85
D. terazosin + enalapril: target 130/80
E. ramipril + amlodipine: target 130
Case B: A 77 y.o. diabetic man, former-smoker, has BMI of 28, and average home BP of 158/91 mmHg. History includes transient ischemic attack when 74. No clinical evidence of carotid insufficiency; LVEF 46%. He takes aspirin 100mg daily, furosemide and metoprolol for NYHA-class-1 heart failure; perindopril and felodipine; acarbose, metformin & sitagliptin. HbA\(_1c\) 61 mmol/mol (7.6%), serum Na\(^+\) 138, K\(^+\) 3.7 mmol/l, urea 6.9 mmol/l, creatinine 122 \(\mu\)mol/l, eGFR 50 ml/min. Urinary ACR 34 mg/mmol. To optimize the patient’s CV disease outcomes, you would advise the following action and BP target (mmHg):

A. replace felodipine with diltiazem: target \(< 140/90\)

B. replace metoprolol with carvedilol: target \(< 140\)

C. replace metoprolol with nebivolol: target \(< 130/80\)

D. replace perindopril with candesartan: target \(< 130\)

E. replace perindopril with valsartan: target \(< 120\)
Case C: A 79 y.o. non-diabetic man, former-smoker, has BMI of 26, and home BP mean of 168/65 mmHg. Supine BP 171/64, upright 154/68 mmHg. History of TICA aged 74, and possible transient global amnesia. He has bilateral carotid bruits. Stable angina pectoris for 8 years; LVEF 43%; PCI declined. He takes aspirin + clopidogrel; for NYHA-class-2 heart failure he takes furosemide, nebivolol and eplerenone; and rosvastatin for dyslipidemia. Antihypertensives: valsartan, amlodipine, and terazosin. HbA$_1c$ 48 mmol/mol (6.2%), serum Na$^+$ 138, K$^+$ 4.9 mmol/l, urea 7.4 mmol/l, creatinine 119 µmol/l, eGFR 53 ml/min; urinary ACR 24 mg/mmol. To optimize the patient’s CV disease outcomes, you would pursue the following systolic BP (mmHg):

A. < 160

B. < 150

C. < 140

D. < 130

E. < 120
LIST OF REFERENCES PERTINENT TO THE
(a) Critically appraised trial outcomes
(b) Issues raised by the appraised outcomes


