SPRINT [1]: Evaluation of Intensive <120mmHg vs. Standard <140mmHg Blood Pressure Targets

Is more intensive BP control in select high-risk patients (e.g. no diabetes or stroke history) beneficial?

Or … "Is 120 the new 140?"

BOTTOM LINE - *SPRINT*

- A lower BP target of <120mmHg versus a standard target of <140mmHg in those at high CV risk, but without diabetes or stroke, resulted in **a trade-off between benefit & harm**. {Mean $_{automated}$ BP achieved at 1 yr: **121/69** vs **136/76**.}
- **Benefits**: The intensive group experienced lower rates of fatal and non-fatal CV events (i.e., 1° outcome = MI, other ACS, stroke, HF, or death from CV causes): 5.2% vs. 6.8%; NNT=63/3.3yr; there was also ↓HF NNT=125, CV death NNT=167, all-cause mortality NNT=83, and the 1° composite plus all-cause mortality NNT=53 (all over 3.3yrs).
- **Harms**: intensive treatment was shown to cause higher risk of adverse events {e.g. hypotension NNH=100, serious adverse event related to the intervention NNH=45, electrolyte abnormalities NNH=125, and acute renal failure NNH=63 (all over ~3.3yrs)}. With higher rate of clinician monitoring in trial, the impact of harms was likely less than real world.
- **An intensive SBP target of <120mmHg is an option in select antihypertensive patients. Careful consideration should be given to the balance of potential benefits and harms with a process of shared decision making.**

Should we target an SBP < 120 mmHg?

In FAVOUR of an SBP target <120mmHg

1) **The potential benefits are clinically meaningful.** This trial showed a statistically significant benefit in the primary, a composite of cardiovascular events and all-cause mortality in patients using the more intensive SBP regimen.
   - *primary CV composite*: **NNT** = 63/3.3 yrs
   - *all-cause mortality*: **NNT** = 83/3.3 yrs
2) **The CV and mortality benefit may make it worth trouble shooting tolerability and adverse event risks for some patients.**

Caveats

- Mean SBP in the intensive group was 121mmHg, but remember that half of the intensive arm, by definition, was above the mean (ie. did not achieve the target BP; important for contextualization.)
- Any consideration of BP targets carries the assumption that BP measurement is accurate and related to the data that informed the target. Office BPs are often done less than ideally predisposing them to be higher than done in trials. {SPRINT: automated system, unattended, and after 5 minutes quiet rest.}

Who may be suitable for the <120mmHg target?

- Those who have a Framingham risk of >15% but not a high degree of comorbidity
- Those who achieve such BP control, without requiring a high number of antihypertensives and do not have difficulty tolerating adverse effects of therapy

Who may not be suitable?

- Those with type-2 **diabetes**, history of **stroke**, proteinuric **kidney** disease or **heart failure** EF < 35%/recent.
- Those who are institutionalized, or older & very frail
- Those requiring more than 3 antihypertensives to get to target. Would be reasonable to be less stringent with targets and cognisant of potential harms.
- Those who do not tolerate antihypertensives well
- Those at risk for falls from postural hypotension
  Link/**Criteria**: http://www.rxfiles.ca/rxfiles/uploads/documents/OrthoHypo-QandA.pdf
- Those who through shared decision making determine that benefits are not worth the added risk, effort and cost associated with the intervention

AGAINST an SBP target <120mmHg

1) **There are potential harms which must be weighed against the potential benefits**, including:
   - **serious adverse events (SAE) related to the intervention** * 4.7% vs 2.5% — **NNH**=45 /3.3 yrs
     - syncope 1.4% vs 0.6% — **NNH**=83 /3.3 yrs
     - hypotension 1.8% vs 0.8% — **NNH**=100 /3.3 yrs
     - electrolyte abnormality — **NNH**=200 /3.3 yrs
     - acute renal failure — **NNH**=63 /3.3 yrs
     - more CKD progression — **NNH**=37 /3.3 yrs
2) **There are real-world drawbacks to pursuing aggressive targets.** More medications (mean 2.8 vs 1.8) were needed to reach the more aggressive target. This means ↑ monitoring, ↑ cost, and ↑ risk of polypharmacy, SAE and drug interactions. (System adjustments needed to support.)
3) **One needs to consider results from previous trials.**
   - **JATOS** [2] and **VALISH** [3] did not find benefit in reducing SBP below 140mmHg in patients with BP from 140 – 150 or 160mmHg. Similarly, a **Cochrane** review did not find benefit in reducing SBP below 140mmHg. [4]
   - **ACCORD-BP** [5] trial showed no difference in 1° outcome CV events for T2DM patients assigned to SBP <120mmHg vs <140mmHg. The annual rate of stroke, a 2° outcome, was reduced (NNT=92/4.7yrs).
   - Previous data has found reducing diastolic BP below 60mmHg may increase risk in patients with CV disease (i.e. a J-curve effect [6,7,8]).
4) **This trial has design issues which may bias results or limit our ability to apply its findings.**
   - The open-label nature of the trial
   - Stopping trial early limits evaluation of long term safety (benefit vs harm)
   - The exclusion of institutionalized adults, as well as those with a history of stroke, diabetes, or recent cardiovascular disease symptoms.
   - Select population. Mean Framingham risk was ~20%/10year (high risk), benefit vs harm may differ in patients with low CV risk.
   - The trial's method of measuring BP is likely to result in lower readings than in the "real-world".
5) **Choice of agent may matter**. (e.g. doxazosin ALLHAT associated with harm relative to diuretic or ACEI as initial therapy.) *Intensive* patients received **more ACEI/ARBs** 77% vs 55% **& thiazides** 55% vs 33% (chlorthalidone).

* SAE defined as an event that was fatal or life threatening, resulting in significant or persistent disability, requiring or prolonging a hospitalization, or was an important medical event that the investigator judged to be a significant hazard or harm to the participant that may have required medical or surgical intervention to prevent one of the other events listed above.

BACKGROUND [1, 9,10,11,12]

- RCTs have shown that a reduction in BP in high risk hypertensive individuals results in ↓incidence of CVD, CAD, CHF, stroke, and CKD, regardless of a patient's age, race, gender or severity of HTN. However, treatment targets for SBP remain uncertain.
- CHEP [2015] Blood Pressure Targets: Standard <140/90mmHg; Diabetes <130/80mmHg; CKD <140/90mmHg; >80yrs = <150/90mmHg

TRIAL BACKGROUND AND EXECUTION

DESIGN: Randomized, controlled, open-label trial, ITT analysis, multisite; funding provided by NHLBI / NIH

INTERVENTION: Participants were randomized into intensive therapy targeting SBP <120 mmHg, or standard therapy, targeting SBP <140 mmHg. Aim of study was to evaluate *treatment strategy*, not a specific drug regimen (use of **SPRINT** formulary drugs was encouraged but not required – example **SPRINT** formulary drugs: chlorthalidone, furosemide, spironolactone, lisinopril, losartan, azilsartan, diltiazem, amlodipine, metoprolol, atenolol, hydralazine, guanfacine, doxazosin – full list available on page 29 of trial supplementary appendix). Lifestyle modification was encouraged.

INCLUSION: Must have met ALL of the following: **≥50yrs**, **SBP 130 to 180mmHg** (or 130 – 170mm Hg on up to 2 medications; 130 – 160 mm Hg on up to 3 medications; 130 – 150 mm Hg on up to 4 medications), and **↑CV Risk** e.g. ≥1 of: clinical or subclinical CVD (other than stroke), CKD with eGFR 20 to 60mL/min, Framingham Risk ≥15%, or age ≥75yrs. No DBP inclusion criteria.

EXCLUSION: diabetes, hx of stroke, residence in a nursing home (persons residing in an assisted living or retirement community are eligible if they meet the other criteria), pregnancy, polycystic kidney dx, ESRD (eGFR <20mL/min/1.73m^2), known 2^o cause of HTN with safety concerns, hospitalization for unstable angina (within last 3 months); symptomatic HF within last 6 months, LVEF <35%; 1 min standing SBP <110mmHg (not applicable if wheelchair use); proteinuria – 24h urinary protein excretion ≥1g/day or urinary albumin excretion ≥ 600mg/day; arm circumference too large/small for accurate BP measurements, any actions likely to limit adherence

POPULATION at baseline: **n= 9,361**: Age 67.9 ± 9yrs; ~64% ♂; ~28% CKD; ~20% CVD clinical or subclinical; ~61% Framingham Risk ≥15%; Framingham Risk Score over 10 years: ~20.1% ± 10.8%

- Race/Ethnic Group: ~58% non-hispanic white; ~30% non-hispanic black; ~10% hispanic; ~2% other
- Baseline BP (mmHg): **SBP ≈ 139.7±15; DBP ≈78±12;**
  Distribution of SBP: ~33% ≤132mmHg; ~32% >132mmHg to <145mmHg; ~34% ≥145mmHg
- eGFR: ~72mL/min/1.73m^2
- TC = 2.15±0.46mmol/L; HDL = 0.60±0.16mmol/L; TG = 1.41±1.05mmol/L; FPG = 5.5±0.75mmol/L; LDL not reported
- Statin use ~43%; current smoker ~13%; aspirin use ~51%; antihypertensives 1.8 ± 1 drugs per patient; ~9% of patients were not using any antihypertensives.
- BMI ≈ 29.8±5.8 kg/m^2

GENERAL

SPRINT followed the same general treatment targets as **ACCORD-BP**, but had many differences e.g. larger sample size (n=9361 vs. 4733), exclusion of pts with DM, inclusion of pts at higher CV risk (i.e. CKD, older age, dyslipidemia).

NHLBI **stopped the trial earlier than expected** due to identified survival benefit for those patients assigned to the lower BP target. {The Drug Safety & Monitoring Board (DSMB) found that the benefits of aggressive BP treatment outweighed risks of treatment.}

RESULTS

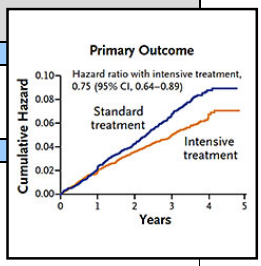
follow-up: median 3.26years (stopped early; planned: mean 5 years)

TABLE 1: BP ACHIEVED AND ANTIHYPERTENSIVE USE

MEAN BP ACHIEVED	INTENSIVE TX (<120MMHG) n=4,678	STANDARD TX (<140MMHG) n=4,683	COMMENTS
Mean SBP achieved (1 yr)	121.4mmHg	136.2mmHg	Note: for the standard group, antihypertensives were removed from the regimen if SBP was sustained below 135mmHg. This was to maintain difference between intervention & control groups.
Mean SBP achieved (over entire study period)	121.5mmHg	134.6mmHg	
Mean DBP achieved (1 yr)	68.7mmHg	76.3mmHg	
# of antihypertensives - *mean*	*2.8*	*1.8*	Distribution of drug classes similar between groups
0	2.7%	11.3%	
1	10.5%	31.1%	
2	30.5%	33.3%	
3	31.8%	17.2%	
4+	24.3%	6.9%	
ARB or ACEI	77% ARB 40%; ACEI 37%	55%	Drug choices mostly in line with guidelines. "Others": no patients on aliskiren, ~10% vs ~5% on alpha blockers e.g. doxazosin, ~2 vs ~1% on centrally acting drugs e.g. clonidine, ~7% vs 2% on vasodilators e.g. hydralazine
Diuretic	67% mainly chlorthalidone (thiazide)	43%	
CCBs	57% mainly amlodipine	35%	
Beta-blockers	41% mainly metoprolol, atenolol	31%	
Others	Up to 10%	Up to 6%	

TABLE 2: EFFICACY & SAFETY 1° & 2° OUTCOMES

CLINICAL ENDPOINTS	INTENSIVE TX (<120MMHG) n=4,678	STANDARD TX (<140MMHG) n=4,683	HR (95% CI)	ARR/ARI	NNT/NNH /3.3YRS	COMMENTS
PRIMARY ENDPOINT						
Composite outcome of MI, other ACS, stroke, HF, or death from CV cause	5.2% (n=243)	6.8% (n=319)	0.75 (0.64-0.89)	↓1.6%	63	
SECONARY ENDPOINTS						
MI	2.1% (n=97)	2.5% (n=116)	0.83 (0.64-1.09)	–	–	
Other ACS	0.9% (n=40)	0.9% (n=40)	1.00 (0.64-1.55)	–	–	
Stroke	1.3% (n=62)	1.5% (n=70)	0.89 (0.63-1.25)	–	–	
HF	1.3% (n=62)	2.1% (n=100)	0.62 (0.45-0.84)	↓0.8%	125	
Death from CV cause	0.8% (n=37)	1.4% (n=65)	0.57 (0.38-0.85)	↓0.6%	167	
All-cause mortality	3.3% (n=155)	4.5% (n=210)	0.73 (0.60-0.90)	↓1.2%	83	
1° Outcome or death	7.1% (n=332)	9.0% (n=423)	0.78 (0.67-0.90)	↓1.9%	53	
RENAL OUTCOMES – For patients with eGFR >60mL/min/1.73m^2 at baseline						
≥30% ↓ in eGFR to <60mL/min/1.73m^2	3.8% (n=127/3332)	1.1% (n=37/3345)	3.49 (2.44-5.10)	↑2.7%	37	Requires further analysis due to early trial termination



Trial excluded pts with history of stroke or TIA as well as diabetes

TABLE 3: ADVERSE EVENTS

ADVERSE EVENTS	INTENSIVE TX (<120MMHG) n=4,678	STANDARD TX (<140MMHG) n=4,683	HR	p VALUE	ARR/ARI	NNT/NNH /3.3YRS	COMMENTS
Serious Adverse Event (SAE)	38.3% (n=1793)	37.1% (n=1736)	1.04	0.25	–	–	
CONDITIONS OF INTEREST – Serious AEs and Monitored Clinical Events							
Acute Renal Failure (AKF)	4.1% (n=193)	2.5% (n=117)	1.66	<0.001	↑1.6%	63	↑ARF may have been due to ↑use of diuretics and ACEIs/ARBs in intensive group. No significant difference between tx groups regarding injurious falls or bradycardia. No difference in rate of hyperkalemia.
Electrolyte Abnormality	3.1% (n=144)	2.3% (n=107)	1.35	0.02	↑0.8%	125	
Hyponatremia <130mmol/L	3.8% (n=180)	2.1% (n=100)	1.76	<0.001	↑1.7%	59	
Hypernatremia >150mmol/L	0.1% (n=6)	0% (n=0)	-	0.02	↑0.1%	1000	
Hypokalemia <3mmol/L	2.4% (n=114)	1.6% (n=74)	1.50	0.006	↑0.8%	125	
Hypotension	2.4% (n=110)	1.4% (n=66)	1.67	0.001	↑1.0%	100	
Orthostatic hypotension	16.6% (n=777)	18.3% (n-857)	0.88	0.01	↓1.7%	59	
+ with dizziness	1.3% (n=62)	1.5% (n=71)	0.85	0.35	–	–	
Syncope	2.3% (n=107)	1.7% (n=80)	1.33	0.05	↑0.6%	167	
Serious Adverse Events Related to the Intervention*	4.7% (n=220)	2.5% (n=118)	1.88	<0.001	↑2.2%	45	

*Data regarding "Serious Adverse Events Related to the Intervention" is provided in the online Supplementary Appendix to the SPRINT publication.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES [1, 3, 4, 5, 6, 7, 8]

STRENGTHS:

- Important clinical endpoints (e.g. CV death, HF, stroke, MI).
- Large study (n=9361); funded by independent group.
- Diverse population; no significant statistical interactions were observed across subgroups.
  - However, benefits were consistent across only some pre-specified subgroups (i.e. ≥75yrs)[1]; exceptions in sex (male, yes benefits maintained; female, no), baseline BP (≤132mmHg, yes; 133-144, no; ≥145, no), race/ethnicity (nonblack, yes; black, no), and previous CKD or CVD (no hx, yes; previous of either, no). Any differences would be hypothesis driving only.
- Large proportion of elderly ≥75yrs (28.2% in each group) with no upper age limit

LIMITATIONS:

- Trial stopped early (median 3.3yrs) when benefits were deemed to outweigh harms.
- The standard treatment group was monitored and if BP was consistently <135mmHg then medications were changed/withdrawn (by study protocol) to ensure blood pressure in the control group remained higher than the intensive group. In real-world practice, these asymptomatic control-group patients likely would not have had a change in therapy. This withdrawal of medications may have contributed to the difference in endpoints. [1]
- Estimates of frequency of serious AEs (trend toward increase) could have been biased. Clinicians were not blinded to pt treatment group and AEs could be reported at any visit. Intensive tx group patients were seen for unscheduled clinic visits 20-30% more often than those patients in the standard arm → these patients had more opportunity to report AEs. [9]
- Potential for study effect: study patients are generally far more motivated regarding adherence, monitoring, health awareness, AE awareness compared to real world.
- Although the target BP goal was <120mmHg (achieved ~121mmHg), the majority of patients did not consistently remain below this level. This target may be too ambitious to be feasible in regular practice. [9]
- Lack of data on DBP - how low is too low? - given the possible J-curve noted in other studies (e.g., DBP <60-70 has previously shown to increase MI). Note, however, that the mean DBP was not below this range.
- In-study BP monitoring (i.e., 5-min quiet rest prior to measurement; automated, without anyone else in the room) may not represent the BP measured in real world practice. Thus the measured study blood pressure may have been lower than what would have been observed in real-world monitoring. As a result, more aggressive treatment may be required in the real-world to reach the study target, increasing the risk of adverse events.

UNCERTAINITIES:

- To what extent are the results **generalizable** to patients who did not meet the inclusion/exclusion criteria?
  - Of US adults [13]:
    - ⇨Only about 17% of hypertension patients meet the SPRINT eligibility criteria
    - ⇨Only about 8% overall meet the SPRINT eligibility criteria
- Is lower better in all patients? The **J-curve** concept in a high CV risk population (i.e. ↓BP is only beneficial to a certain target and then becomes harmful) may be significant.
- What is the impact on **cognition**? Some pre-specified secondary endpoints (dementia, decline in cognitive function, and small vessel cerebral ischemic disease) remain unreported. [14]
- Will patients in the real-world be able to achieve the needed **adherence** to the intensive medication regimen?
- No specific treatment algorithm regarding medications was used. The **SPRINT** formulary encouraged use of medications with the best evidence, but it was not strictly enforced or followed. From previous studies, **choice of agent may make a difference** (e.g. harm with alpha blocker as initial treatment relative to chlorthalidone ALLHAT). *Intensive* patients received more ACEI/ARBs 77% vs 55% & thiazides 55% vs 33% (chlorthalidone on trial formulary).
- Will the risk-to-benefit ratio hold up over the **long-term**?

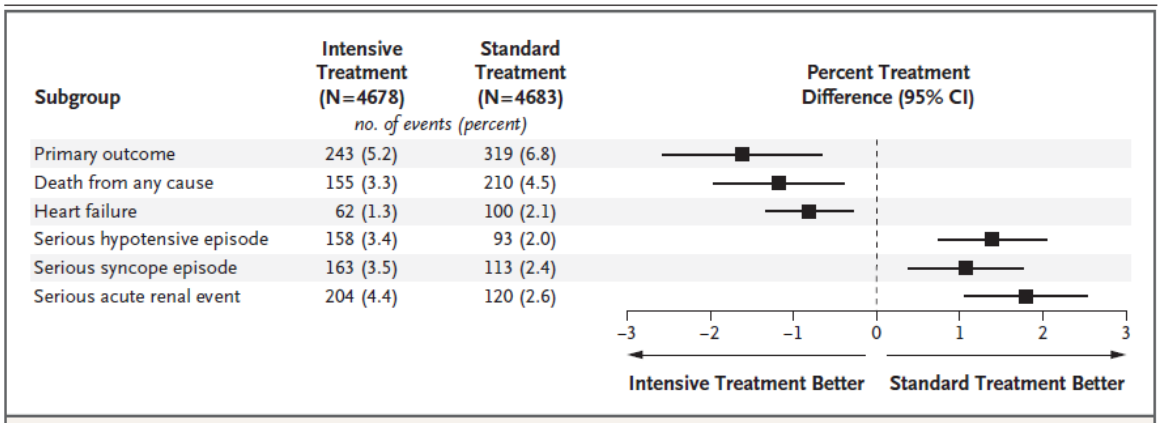


Figure 3. Balancing Efficacy and Safety Outcomes in SPRINT.

In the SPRINT trial, among 9361 selected patients with a systolic blood pressure of 130 mm Hg or more who were randomly assigned to intensive treatment (a systolic blood-pressure target of <120 mm Hg) or standard treatment (a target of <140 mm Hg), intensive treatment resulted in a substantially lower rate of the composite primary outcome of myocardial infarction, other acute coronary syndrome, stroke, heart failure, or cardiovascular death than standard treatment and in lower rates of all-cause death and heart failure. However, intensive treatment was associated with significantly higher rates of serious adverse events related to hypotension, syncope, and acute kidney injury. Data are from the SPRINT Research Group.[31]

RxFiles related links:

- Antihypertensives: Landmark & Recent Trials: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-HTN-trial-summary.pdf
- Hypertension in Older Adults: http://www.rxfiles.ca/rxfiles/uploads/documents/Hypertension%20in%20Older%20Adults%20-%20Highlights.pdf
- Hypertension in the Elderly – Targets & Tips: in CFP Journal May 2014: http://www.cfp.ca/content/60/5/453.full
- **ACCORD-BP** & Lipid Trials Overview: http://www.rxfiles.ca/rxfiles/uploads/documents/ACCORD-BP-Lipid-Trial-Overview.pdf
- Hypertension Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-HTN-trial-summary.pdf
- Orthostatic Hypotension (Postural Hypotension): http://www.rxfiles.ca/rxfiles/uploads/documents/OrthoHypo-QandA.pdf
- Other links: http://www.rxfiles.ca/rxfiles/modules/miscellaneous/search.aspx?for=hypertension

✗ =non-formulary in SK ⊗=not covered by NIHB ☎=Exceptional Drug Status in SK ♂=male **ACEI**=angiotensin converting enzyme inhibitor **ACS**=acute coronary syndrome **AE**=adverse event **AKI**=Acute kidney injury **Anti-HTN**=antihypertensive **ARB**=angiotensin receptor blocker **ARF**=acute renal failure **BMI**=body mass index **BP**=blood pressure **CAD**=coronary artery disease **CKD**=chronic kidney disease **CV**=cardiovascular **DBP**=diastolic blood pressure **DM**=diabetes mellitus **DSMB**=data and safety monitoring board **d/t**=due to **dx**=disease **EF**=ejection fraction **ESRD**=end stage renal disease **HCP**=healthcare professional **HCTZ**=hydrochlorothiazide **HF**=heart failure **HR**=heart rate **HTN**=hypertension MI=myocardial infarction **NNT/H**=number needed to treat/harm **pt**=patient **RCT**=randomized controlled trials **SBP**=systolic blood pressure **T2DM**=type 2 diabetes mellitus

ACKNOWLEDGEMENTS: Contributors & Reviews: Prepared By: Aleina Haines, BSP Candidate 2016; Zack Dumont BSP ACPR; Loren Regier BSP; Alex Crawley BSP. Reviewers included Brent Jensen BSP, Tessa Laubscher MB ChB CCFP FCFP, Margaret Jin PharmD, Lynette Kosar MSc BSP, Aron Nenninger BSc(Pharm), R Basi MD, Roland Halil PharmD.

[1] **SPRINT** Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26;373(22):2103-16. (Supplementary Appendix also published online at http://www.nejm.org/.)
[2] **JATOS** Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). Hypertens Res 2008; 31:2115–2127.
[3] **VALISH**: Ogihara T, Saruta T, Rakugi H, et al. Valsartan in Elderly Isolated Systolic Hypertension Study Group. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. Hypertension. 2010 Aug;56(2):196-202.
[4] Diao D, Wright JM, Cundiff DK, Gueyffier F. Pharmacotherapy for mild hypertension. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD006742. DOI: 10.1002/14651858.CD006742.pub2
[5] **ACCORD** Study Group, Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. N Engl J Med 2010 0: NEJMoa1001286.
[6] Does extreme dipping of nocturnal blood pressure in elderly hypertensive patients confer high risk of developing ischemic target organ damage from antihypertensive therapy?*Kario K,Pickering TG. Arch Intern Med. 2000 May 8; 160(9):1378*
[7] **SHEP** Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (**SHEP**). JAMA 1991;265(24):3255-64.
[8] Kjeldsen SE, Oparil S, Narkiewicz K, Hedner T. The J-curve phenomenon revisited again: **SPRINT** outcomes favor target systolic blood pressure below 120 mmHg. Blood Press. 2016 Feb;25(1):1-3.
[9] Drazen JM, Morrissey S, Campion EW, Jarcho JA. A **SPRINT** to the Finish. N Engl J Med. 2015 Nov 9.
[10] Perkovic V, Rodgers A. Redefining Blood-Pressure Targets - **SPRINT** Starts the Marathon. N Engl J Med. 2015 Nov 9.
[11] Chobanian AV. Time to Reassess Blood-Pressure Goals. N Engl J Med. 2015 Nov 9.
[12] Xie X, MD, Atkins E, Lv J. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Published Online: 07 November 2015.
[13] Bress AP, Tanner RM, Hess R, et al. Generalizability of results from the Systolic Blood Pressure Intervention Trial (**SPRINT**) to the US adult population. J Am Coll Cardiol. 2015 Oct 31.
[14] Jones DW, Weatherly L, Hall JE. **SPRINT**: What Remains Unanswered and Where Do We Go From Here? Hypertension. 2015 Nov 9.

Additional References:

Bress AP, Kramer H, Khatib R, et al. **Potential Deaths Averted and Serious Adverse Events Incurred** from Adoption of the SPRINT Intensive Blood Pressure Regimen in the U.S.: Projections from NHANES. Circulation. 2017 Feb 13.

Chang TI, Evans G, Cheung AK, et al; SPRINT Study Research Group. Patterns and Correlates of Baseline **Thiazide-Type Diuretic Prescription** in the Systolic Blood Pressure Intervention Trial. Hypertension. 2016 Mar;67(3):550-5.

Ortiz E, James PA. **Let's Not SPRINT to Judgment** About New Blood Pressure Goals. Ann Intern Med. 2016 Feb 23.

Sexton DJ, Canney M, O'Connell MDL, Moore et al. **Injurious Falls and Syncope** in Older Community-Dwelling Adults Meeting Inclusion Criteria for SPRINT. JAMA Intern Med. 2017 Jul 17.

Williamson JD, Supiano MA, Applegate WB, et al. **Intensive vs standard blood pressure** control and cardiovascular disease outcomes in **adults aged 75 years**: a randomized clinical trial (**SPRINT**). JAMA. doi:10.1001/jama.2016.7050.