

# Hypertension

## On the Border of Guidelines and Personalized Medicine

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# Disclosures

None pertaining to this talk

Regeneron/Sanofi Speaker Board  
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# Background

- Hypertension affects approximately 1 billion adults worldwide.
- Among persons  $\geq 50$  yo, isolated systolic HTN is the most common form of hypertension
- As humans age, systolic blood pressure becomes more important than diastolic blood pressure as an independent risk predictor for coronary events, stroke, heart failure, and ESRD



# High Blood Pressure is important

- Suboptimal blood pressure is the primary attributable risk for death worldwide
  - Accounting for:
    - 62% of cerebrovascular disease
    - 49% of ischemic heart disease
    - > 7 million deaths per year



## Background

- Clinical trials have shown that treatment of hypertension reduces the risk of cardiovascular disease outcomes
  - Incident stroke (by 35 to 40%)
  - Myocardial infarction (by 15 to 25%)
  - Heart failure (by up to 64%)

- The benefits of successful treatment are substantial!!
  - 96% reduction in cardiovascular events over 18 months with use of triple antihypertensive regimens in patients with severe hypertension
    - compared with placebo

## Unfortunately, doctors aren't very good at controlling BP

MOTHER GOOSE & GRIMM by Mike Peters



## Background

Hypertension control to a blood pressure <140/90mmHg is achieved in only about 50% of the general population in the United States

- National Health and Nutrition Examination Survey (NHANES)
  - In participants being treated for HTN, only 53% were controlled to <140/90 mm Hg.
  
- Framingham Heart Study
  - Only 48% of treated participants were controlled to <140/90 mm Hg
  - <40% of elderly participants (>75 years of age) were at a goal blood pressure.



## Why can't we control hypertension?



## Why Can't We Control HTN?

- 1) Pseudo-Resistance
- 2) Patient Lifestyle
- 3) Undiagnosed Condition
  - “Secondary” HTN
- 4) Ineffective Drug Choices
- 5) Treatment Inertia/Lack of Recognition



## It's not all the doctors fault: Pseudo-Resistance

- Poor adherence to meds
- Incorrect BP measuring technique
- White Coat HTN



## Poor Adherence To Meds



- ~40% of patients with newly diagnosed HTN will discontinue their BP meds during the first year of treatment

## Incorrect BP measuring technique

- Two most common mistakes:
  - Wrong size cuff
    - Too small → Too high
  - Measuring the blood pressure before letting the patient sit quietly



## White Coat HTN

- 38% of patients with resistant HTN actually only had “White Coat HTN”



## It's not all the doctors fault: Causes of Resistance

- 1) Pseudo-Resistance
- 2) Patient Lifestyle
- 3) Undiagnosed Condition  
“Secondary” HTN
- 4) Ineffective Drug Choices
- 5) Treatment Inertia/Lack of Recognition




SIPRESS  
 "I'm going to take your blood pressure, so try to relax and not think about what a high reading might mean for your chances of living a long, healthy life."

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## Causes of Resistance


- Patient Lifestyle
  - Salt
  - Diet
  - Inactivity
  - Obesity



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392W  
 "You've got the blood pressure of a teenager - who lives on junk food, TV and the computer."

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## Sodium


- Reduced sodium intake:
  - Improves HTN control
  - Save \$10-24 billion health care dollars annually
  - Reduces CV clinical events
    - By 21-41%
  - Decrease annual deaths from any cause by 44,000 to 92,000



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## Causes of Resistance

- 1) Pseudo-Resistance
- 2) Patient Lifestyle
- 3) Undiagnosed Condition  
 "Secondary" HTN
- 4) Ineffective Drug Choices

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## Secondary Hypertension

- Only 5-10% of the total hypertensive population has secondary hypertension
  - 2-5 million people in the U.S.

## Undiagnosed Conditions: Most Common

- Primary Aldosteronism
- OSA
- Drug-Induced

## Why Can't We Control HTN?

- 1) Pseudo-Resistance
- 2) Patient Lifestyle
- 3) Undiagnosed Condition
  - “Secondary” HTN
- 4) Ineffective Drug Choices
- 5) Treatment Inertia/Lack of Recognition

## HTN Treatment is important for even “mild” HTN

- Blood pressure lowering therapy is likely to prevent stroke and death in patients with uncomplicated grade 1 hypertension
  - The average blood pressure reduction was only ~3.6/2.4 mm Hg.
  - Over 5 years, odds ratios were:
    - 0.72 (CI, 0.55 to 0.94) for strokes
    - 0.75 (CI, 0.57 to 0.98) for cardiovascular deaths
    - 0.78 (CI, 0.67 to 0.92) for total deaths

Now we know why it is hard to control, but what should we aim for?

## Blood Pressure Goals

### What is the BEST Blood Pressure?

- Observational studies have shown a progressive increase in CV risk as systolic blood pressure rises above 115 mm Hg
- Previously, the available evidence from RCTs in the general population of hypertensive patients only documented a benefit of achieving SBP <150mm Hg
  - Limited data concerning lower BP targets

### Blood Pressure Goals: Background

- In 2003, JNC-7 established BP goals of <140/90 mm Hg for the general population and <130/80 mm Hg for patients with diabetes and/or chronic kidney disease

## Blood Pressure Goals: Background

- Soon thereafter, the JNC-8 committee was constituted
- The NHLBI then decided that it no longer wished to be in the business of guidelines
  - No other organizations rushed in to provide alternative sponsorship to the previously organized writing committee.
- The result was that the writing committee of what was to have been JNC-8, decided to go it alone and publish their report with recommendations anyway.
  - This appeared in 2014, 11 years after JNC-7.

## Blood Pressure Goals: Background

- The “JNC-8” panel recommendations were confined to 3 questions:
  - The level of BP at which treatment should be initiated
  - The BP goal of therapy
  - The selection of the appropriate drug therapy

## “JNC 8”

- Hypertensive persons > 60 have a BP goal of <150/90 mm Hg
- Hypertensive persons 30 -59yo have a diastolic goal of <90 mm Hg
- Because of insufficient evidence, expert opinion suggests a goal of <140/90 for:
  - <60yo
  - Diabetes
  - Non-diabetic chronic kidney disease
- No recommendations regarding:
  - Resistant or Secondary HTN
  - How to measure BP
  - Does not recommend B Blocker
  - Etc.

## “JNC 8”

- For non-black patients:
  - Initiate drug treatment with an ACEi, ARB, CCB, or thiazide-type diuretic
- For Black patients:
  - CCB or thiazide-type diuretic is recommended as initial therapy
    - Even for black patients with DM
- “There is moderate evidence to support initial or add-on antihypertensive therapy with an ACEi or ARB in persons with CKD to improve kidney outcomes.”



## Goals are Controversial

- Different BP target for patients over 60
- The JNC-8 panel recommendations were claimed to be entirely “evidence-based.”
  - However, of the 10 recommendations for hypertension management, only 4 were based on randomized controlled trials evidence, and the remaining 6 were based on “expert opinion.”

- The recommendation of a higher BP target for the >60yo contradicted hypertension guidelines that appeared in 2013 to 2014:
  - European Society of Hypertension
  - European Society of Cardiology
  - American Heart Association
  - American College of Cardiology
  - Centers for Disease Control and Prevention
  - American Society of Hypertension
  - International Society of Hypertension
- All supported a treatment goal of <140/90mm Hg in all pts
  - Except for pts >80yo, where targets relaxed in some guidelines

- Controversy over what to do with the huge number of hypertensive patients 60-80yo
  - So controversial that that 5 members of the “JNC-8” Writing Committee published a “minority report” dissociating themselves from the JNC-8 panel recommendations on relaxed BP goals for pts >60yo
    - “Unprecedented”

If you treated the ~80,000 older pts in the study population who were affected by the change in targets to a stricter “JNC 7” SBP goal of <140mmHg, you could potentially avert ~ 8,000 cardiovascular events over 10 yrs

- In the NCDRI database (>1million patients)
  - Among the patients for whom goal achievement changed:
    - 23.2% had a prior stroke or TIA
    - 64.6% had CAD
    - Average Framingham risk score was  $8.5 \pm 3.2\%$
    - 10-year ASCVD risk score was 28.0% ( $\pm 19.5\%$ )
    - Equivalent to a NNT of 10 to 11 patients to prevent 1 cardiovascular event, over 10 years

- Where are we now?

## ACCORD Trial

## ACCORD Trial

- The rate of major CV events was similar with a systolic blood-pressure target of <120 mm Hg vs. <140 mm Hg
- Wasn't totally negative:
  - The rate of stroke was lower with the target of <120 mm Hg

## SPS3 Trial

## SPS3 Trial

- Population: Patients with Hx of stroke
- Compared treatment goals of <130 mmHg vs. <150 mmHg:
- No significant benefit of the lower target with respect to the overall risk of another stroke
  - But again there was a hint of subgroup benefit
    - Hemorrhagic stroke decreased in aggressive arm.

## SPRINT Trial

## SPRINT Trial

- Randomized, controlled, open-label trial
- Conducted at 102 clinical sites in the U.S.
- Sponsored by the NHLBI
- “Does a lower BP level further reduce CV events and all-cause mortality in people with very high CV risk?”



## SPRINT Trial: Results

- NNT
  - To prevent a primary outcome event = 61
  - To prevent death from any cause = 90
  - To prevent death from cardiovascular causes = 172

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## NNT for BP Control

- To prevent 1 stroke in a hypertensive elderly patient over 2 years:
  - NNT = 63
- To prevent 1 CV event over 5 years in a patient with SBP >160, with a thiazide diuretic:
  - NNT = 122

Wright JM, *Cochrane Database Syst Rev.* 2009(3):CD001841.  
Ann Intern Med. 2009;150:396-404.  
Pearce KA et al. *Am J Hypertens.* 1998;11:618-629.  
Wysong CS et al. *Cochrane Database Syst Rev.* 2007;(1)  
NEJM 1989;321:129-135.  
Ridker PM et al. *NEJM* 2005;352:1293-1304.  
Berger JS et al *JAMA.* 2006;295:306-313.

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## Adverse Events

- Serious adverse events occurred in excess of 37% in BOTH groups
- Significant increase in serious adverse events “possibly or definitely related to the intervention”
  - Relative risk increase = 88%, P<0.001

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## SPRINT vs. ACCORD

- Identical SBP targets (<120 mmHg vs. < 140 mmHg)
- SPRINT enrolled an older cohort
  - mean age, 68 years, vs. 62 years in ACCORD
  - 28% of participants ≥75 yrs old
- SPRINT relied on more long-acting meds
  - SPRINT used mostly chlorthalidone
  - ACCORD used mostly HCTZ
  - Better 24hr BP control



## SPRINT vs. ACCORD

- ACCORD:
  - Had less statistical power than SPRINT
    - Sample size of the ACCORD trial was only half that of SPRINT (4733 vs. 9361)
    - Had an event rate half of what was expected
      - 2% vs. 4%
    - Showed a (nonsignificant) trend 12% lower risk of its primary outcome
      - 95% confidence interval *included the possibility* of a 27% lower risk
        - which is consistent with the findings of SPRINT



## SPRINT vs. ACCORD

- ACCORD's primary outcome did not include heart failure
  - Did include a higher proportion of events that are less sensitive to blood-pressure reduction
- ACCORD enrolled lower risk cohort
  - Younger
  - No CKD allowed



## SPRINT vs. ACCORD

- Difference in results between the trials could be due to differences in study design or treatment interactions
- ACCORD was 2 x 2 Factorial
  - There may have been an interaction between the arms
  - A re-analysis of ACCORD demonstrated that the arm with intensive BP treatment **with usual glucose control**, compared against standard BP control/standard glucose control, led to improved major CV outcomes
    - HR 0.67 95% CI 0.50-0.91

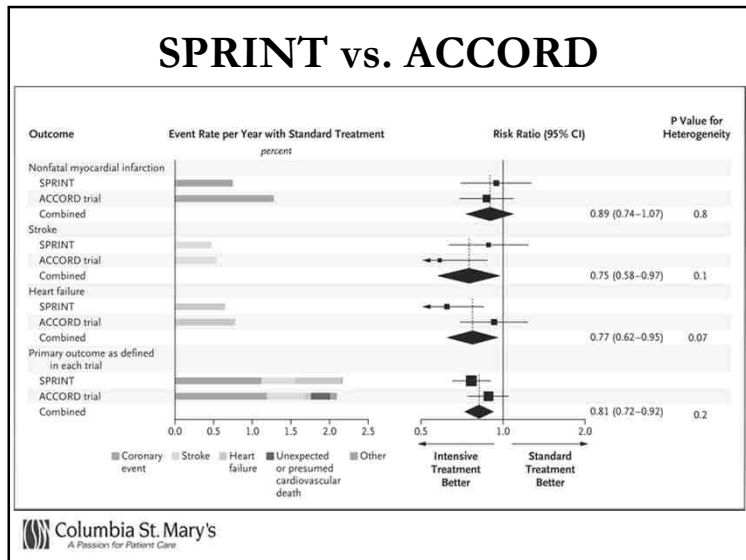


Margolis et al. Diabetes Care 2014; 37(6):1721-8



# What does the totality of data say?

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- ## Lancet Meta-Analysis
- 19 trials including 44,989 participants
    - Not including SPRINT
  - Patients in the more intensive BP-lowering treatment group had mean BP levels of 133/76mmHg, compared with 140/81mmHg in the less intensive treatment group.
  - Intensive blood pressure-lowering treatment led to:
    - 14% reduction in Major Cardiovascular Events (95% CI 4-22)
    - 13% reduction in Myocardial Infarction (CI 0-24)
    - 22% reduction in Stroke (10-32)
    - 10% reduction in Albuminuria (3-16)
    - 19% reduction in Retinopathy progression (0-34)
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- Xie X et al. Lancet 2016

### Another Meta-Analysis

- 123 studies with 613,815 participants for the tabular meta-analysis
  - Included SPRINT.
- Meta-regression analyses showed RR reductions proportional to the magnitude of the blood pressure reductions achieved.

### Another Meta-Analysis

- Every 10<sub>mm</sub> Hg reduction in systolic blood pressure significantly reduced the risk of:
  - Major cardiovascular disease events (RR = 0.80)
  - Coronary heart disease (0.83)
  - Stroke (0.73)
  - Heart failure (0.72)
- Led to a significant 13% reduction in all-cause mortality (HR = 0.87)
  - The effect on renal failure was not significant

### Another Meta-Analysis

“By showing no evidence for a threshold below which blood pressure lowering ceases to work, the findings call for blood pressure lowering based on an individual’s potential net benefit from treatment rather than treatment of the risk factor to a specific target”

**So what does all this mean?**



*“There’s no easy way I can tell you this, so I’m sending you to someone who can.”*

## So What Does This Mean?

- SPRINT looked at a very high risk cohort
- Estimated that only 16.7% of hypertensive patients meet the SPRINT eligibility criteria
  - Only 5% of untreated patients
  - *“Highly selected, high risk”*

SPRINT provides meaningful data to help guide aggressiveness of BP lowering in older people with very high CV risk.

## So:

- Consider that target in those who have similar demographics
  - Age  $\geq 50$  years
  - Systolic blood pressure of 130 to 180 mm Hg
  - Increased risk of cardiovascular events:
    - Clinical or subclinical CV disease other than stroke
    - CKD
      - estimated (eGFR) of 20 - 60 ml per minute per 1.73 m<sup>2</sup> of BSA
    - 10-year CV risk  $\geq 15\%$  by Framingham risk score
    - Age  $\geq 75$  years

**But should all patients  
be  $< 120$ ?**



**No:  
One Target  
Does NOT  
fit all**



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"Bummer of a birthmark, Hal."

- Try to tell your patient that lowering their BP to 120mmHg by taking 3 drugs every day for more than 3 years will reduce stroke and MI from 7/100 to 5/100, but increase their risk for hypotension, falls, AKI, syncope by as much as 88%

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**NNT**

- Primary Outcome = 61
- Heart Failure = 125
- CV Mortality = 167

**NNH**

- AKI = 62
- Electrolyte Abnl = 125
- Syncope = 167

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■ My advice:

- Remember that patients are individuals: genetically, physiologically, psychologically, pathologically, and culturally. There is no one way to treat everyone.
- Assess your patient's level of risk, and treat that risk

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## But Remember:

Reductions in Blood Pressure translate into  
observable decreases in stroke risk within  
months

# The End

