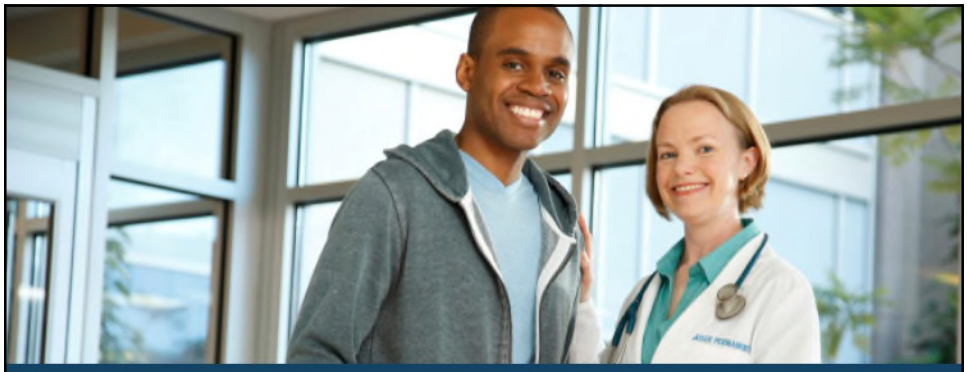

Hypertension Guideline Continued Post JNC 8: Eligible Studies

Joel Handler, MD

Former National Kaiser Permanente Hypertension Lead

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Guideline Inclusion JNC 8 vs ACC/AHA Methodology

- JNC 8: "The panel limited its evidence review to randomized controlled trials because they are less subject to bias than other study designs and represent the gold standard for determining efficacy and effectiveness." IOM 2013
- ACC/AHA "For the majority of topics literature searches focus mostly on randomized controlled trials, and is expanded to nonrandomized studies, case studies, and opinion documents until the evidence base is sufficient." ACC/AHA Methodology Manual 2010

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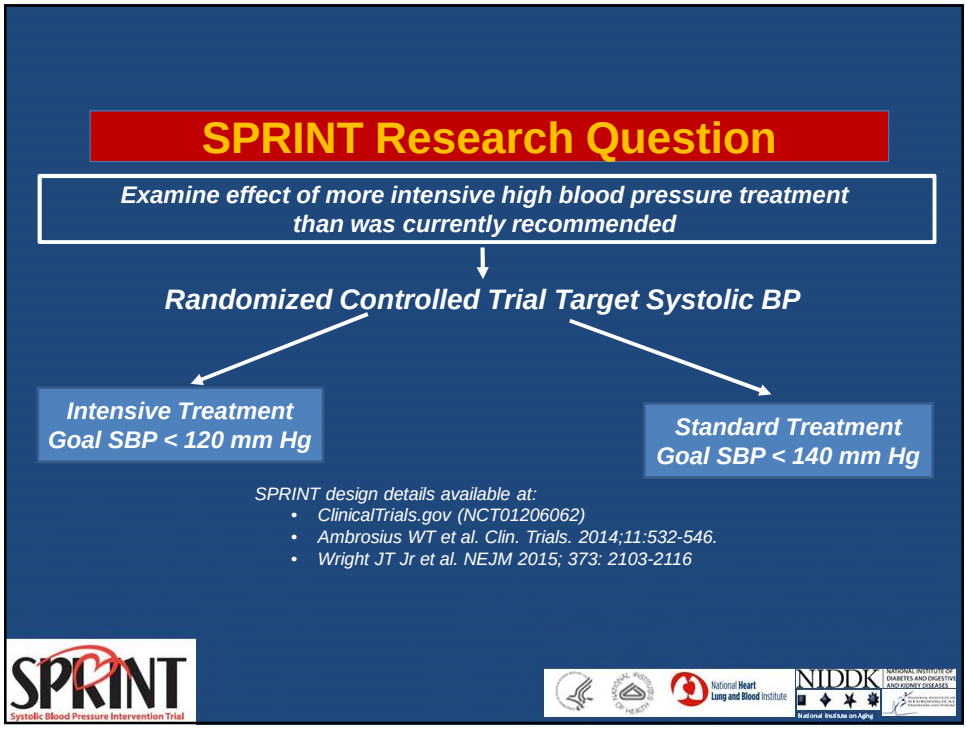


Major Inclusion Criteria

- ***≥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/1.73m^2***
  - ***10-year CVD risk ≥ 15% by Framingham Risk Score***
  - ***Age ≥ 75 years***

At least one

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/1.73m^2 (MDRD)*
- *Adherence concerns*

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/1.73m^2)*
- *CVD (CVD vs. no prior CVD)*
- *Level of BP (Baseline SBP tertiles: ≤132, 133 to 144, ≥145 mm Hg)-*

Primary Outcome and Primary Hypothesis

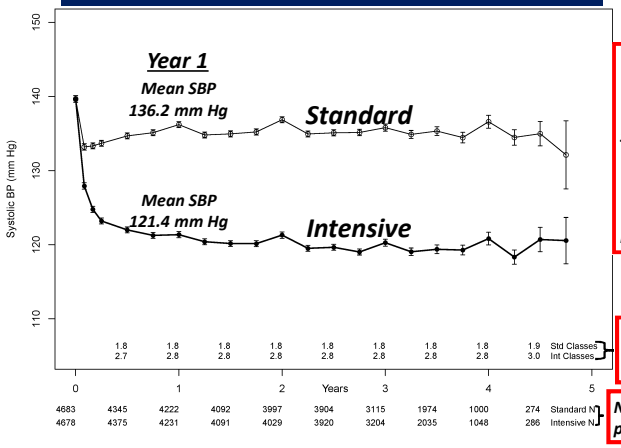
- ***Primary outcome***
  - ***CVD composite: first occurrence of***
    - ***Myocardial infarction (MI)***
    - ***Acute coronary syndrome (non-MI ACS)***
    - ***Stroke***
    - ***Acute decompensated heart failure (HF)***
    - ***Cardiovascular disease death***
- ***Primary hypothesis****
    -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

Location of 102 SPRINT Clinical Centers

Also Supported by 15 CTSAs

Systolic BP During Follow-up



Average SBP (During Follow-up)

Standard: 134.6 mm Hg

Intensive: 121.5 mm Hg

Average number of antihypertensive medications

Number of participants

SPRINT

Letters to the Editor

The NEW ENGLAND JOURNAL of MEDICINE

HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS

CORRESPONDENCE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The authors reply: Pfeffer asks how often antihypertensive medications were discontinued in asymptomatic participants in the standard-treatment group who had a systolic blood pressure of less than 130 mm Hg or less than 135 mm Hg. Antihypertensive therapy in the standard-treatment group often required adjustment; 87% of participants required at least one reduction in the dose of medication to maintain systolic blood pressure in the range of 135 to 139 mm Hg. Withdrawal of medication was required in less than 7.5% of participants. Such adjustments, although not standard in clinical practice, were required to adequately test the SPRINT hypothesis.

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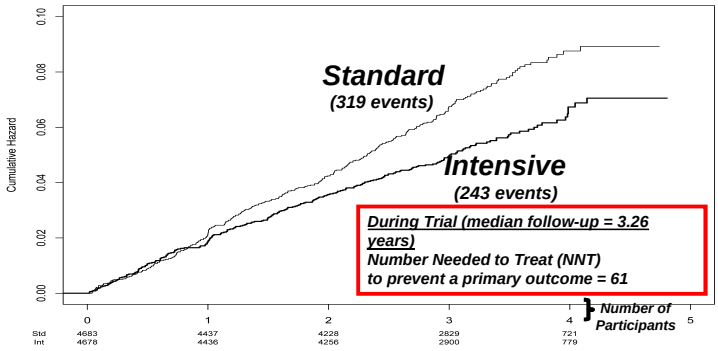
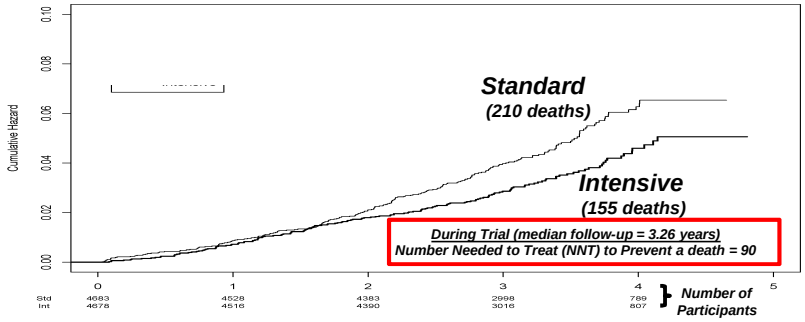
SPRINT Primary Outcome Cumulative Hazard

Hazard Ratio = 0.75 (95% CI: 0.64 to 0.89, p<0.001)



All-cause Mortality Cumulative Hazard

Hazard Ratio = 0.73 (95% CI: 0.60 to 0.90, p= 0.003)

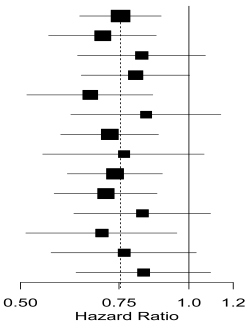


Primary Outcome Experience in the Six Pre-specified Subgroups of Interest

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

*Treatment by Subgroup Interaction

*Unadjusted for multiplicity



Serious Adverse Events* (SAE) During Follow-up

	Number (%) of Participants		
	Intensive	Standard	HR (P Value)
All SAE reports	1793 (38.3)	1736 (37.1)	1.04 (0.25)
SAEs associated with Specific Conditions of Interest			
Hypotension	110 (2.4)	66 (1.4)	1.67 (0.001)
Syncope	107 (2.3)	80 (1.7)	1.33 (0.05)
Injurious fall	105 (2.2)	110 (2.3)	0.95 (0.71)
Bradycardia	87 (1.9)	73 (1.6)	1.19 (0.28)
Electrolyte abnormality	144 (3.1)	107 (2.3)	1.35 (0.020)
Acute kidney injury or acute renal failure	193 (4.1)	117 (2.5)	1.66 (<0.001)

**Fatal or life threatening event, resulting in significant or persistent disability, requiring or prolonging hospitalization, or judged important medical event.*

Original Investigation

Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years
A Randomized Clinical Trial

Jeff D. Williamson, MD, MHS; Mark A. Supiano, MD; William B. Applegate, MD, MPH; Dan R. Berlowitz, MD; Ruth C. Campbell, MD, MSPH; Glenn M. Chertow, MD; Larry J. Fine, MD; William E. Haley, MD; Amret T. Hawfield, MD; Joachim H. Ix, MD, MAS; Dalane W. Kitzman, MD; John B. Kostis, MD; Marie A. Krousel-Wood, MD; Lenore J. Launer, PhD; Suzanne Oparil, MD; Carlos J. Rodriguez, MD, MPH; Christianne L. Roumie, MD, MPH; Ronald I. Shorr, MD, MS; Kaycee M. Sink, MD, MAS; Virginia G. Wadley, PhD; Paul K. Whelton, MD; Jeffrey Whittle, MD; Nancy F. Woolard; Jackson T. Wright Jr, MD, PhD; Nicholas M. Pajewski, PhD; for the SPRINT Research Group

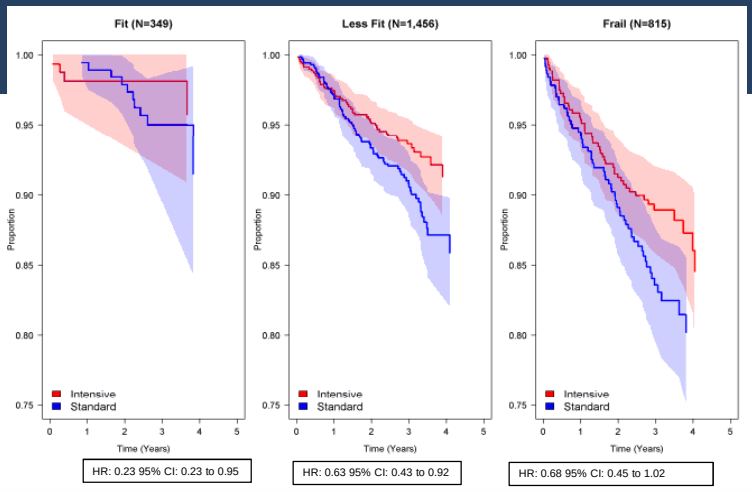
IMPORTANCE The appropriate treatment target for systolic blood pressure (SBP) in older patients with hypertension remains uncertain.

OBJECTIVE To evaluate the effects of intensive (<120 mm Hg) compared with standard (<140 mm Hg) SBP targets in persons aged 75 years or older with hypertension but without diabetes.

Editorial

Supplemental content at jama.com

Kaplan-Meier Survival Curves for SPRINT Primary Outcome by Frailty Status



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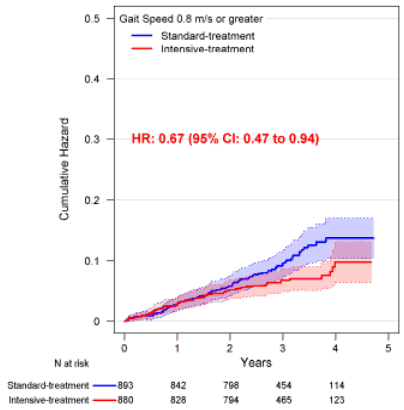
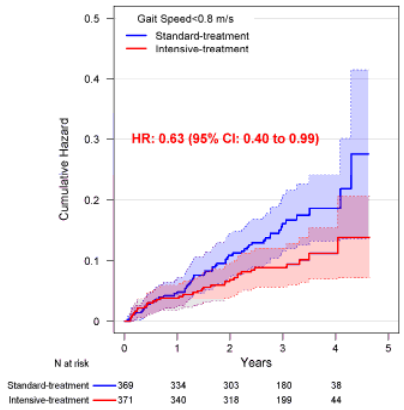
Cumulative Hazards for SPRINT Primary Outcome by Gait Speed





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Serious Adverse Events* (SAE) During Follow-up In Participants Over Age 75

	Number (%) of Participants		
	Intensive	Standard	HR (P Value)
All SAE reports	640 (48.6)	638 (48.4)	1.00 (0.93)
SAEs associated with Specific Conditions of Interest			
Hypotension	36 (2.7)	24 (1.6)	1.49 (0.13)
Syncope	46 (3.5)	37 (2.8)	1.24 (0.33)
Injurious fall	70 (5.3)	79 (6.0)	0.88 (0.42)
Bradycardia	41 (3.1)	43 (3.3)	0.94 (0.79)
Electrolyte abnormality	58 (4.4)	41 (3.1)	1.40 (0.10)
Acute kidney injury or acute renal failure	75 (5.7)	54 (4.1)	1.38 (0.07)

Presented
Gerontological Soc of Am Meeting, Nov, 2015

*Fatal or life threatening event, resulting in significant or persistent disability, requiring or prolonging hospitalization, or judged important medical event.

BP Measurement in SPRINT: Automated Office BP (AOBP)

- Visit BP was the average of 3 seated office BP measurements obtained using an automated measurement device: Omron 907XL.
- Appropriate cuff size was determined by arm circumference.
- Participant was seated with back supported and arm bared and supported at heart level.
- Device was set to delay 5 minutes to begin 3 BP measurements – research staff was trained to push start button, but the protocol did not address room attendance by staff (38 sites alone, 25 not)
- BP was also measured 1 min after standing at screening, baseline, 1, 6, and 12 months, and annually thereafter. While standing, participants were asked about symptoms of hypotension.

Summary and Conclusions

- **SPRINT now fills the deficit of RCT outcome data on SBP targets below 150 mmHg that led to a majority of a 2014 US guideline panel's recommendation of a less than 150 treatment target in patients over age 60.**
- **SPRINT documented the benefit of a SBP target of < 120 mmHg over one < 140 on CV events (NNT= 61) and total mortality (NNT=90) even in patients over age 75 (NNT= 28 and 41 resp).**
- **SPRINT also established that even in those over age 75, frailty status in non-institutionalized patients did not lessen benefit, and the lower SBP target was at least as well tolerated as in the whole cohort**
- **Overall, benefits of more intensive BP lowering in SPRINT exceeded the potential for harm**
- ***Interestingly, we now have substantially better risk/benefit data for recommending target BPs below 140 in those over age 60 than we have in those less than age 50***

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The Secondary Prevention of Small Subcortical Strokes (SPS3) Study

Blood-pressure Targets in Patients with Recent Lacunar Stroke:

The SPS3 Randomized Trial

SPS3 Study Group, Benavente OR,et al.
Lancet. 2013(Aug 10);382:507-15.

SPS3 Coordinating Center: University of British Columbia, Vancouver, Canada
SPS3 Statistical Center: University of Alabama at Birmingham, US

SPS3 is sponsored by National Institutes of Health - NINDS
NINDS: U01 NS38529

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SPS3 Summary

- N = 3020, mean age 63, mean followup 3.7 yrs
- Eligibility: lacunar stroke documented with sxs and confirmed by MRI within 180 days of randomization
- Goal SBP < 150 vs < 130
- Nonsig decrease for all stroke, disabling and fatal stroke, and composite of MI and CVD death
- Annual stroke rate only 2.7 % vs 7% initially predicted
- Rate of intracerebral hemorrhage was decreased 6 vs 16 events, p = 0.03, but representing < 10% of all strokes (22 of 277)

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A Statistically Significant Difference in Recurrent Stroke was not Found

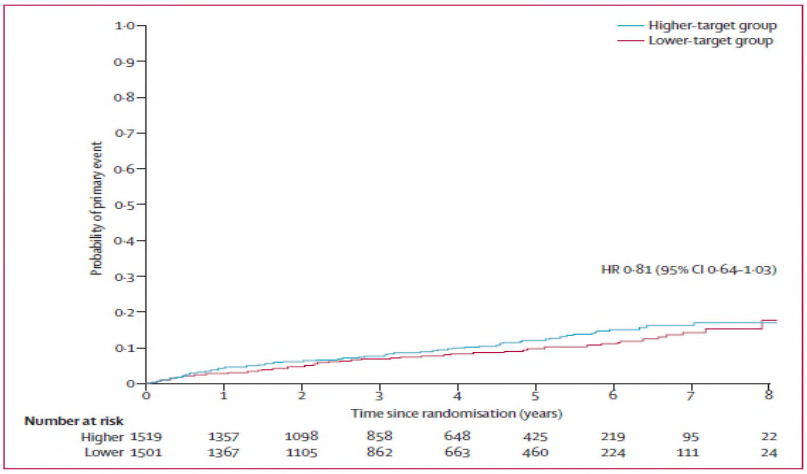

Figure 2: **Probability of patients experiencing a primary event by time after randomisation**
Primary events were all recurrent strokes, myocardial infarction, or vascular death. HR–hazard ratio.

www.thelancet.com Vol 382 August 10, 2013

ORIGINAL ARTICLE

Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Eva M. Lonn, M.D., Jackie Bosch, Ph.D., Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Lisheng Liu, M.D., Prem Pais, M.D., Rafael Diaz, M.D., Denis Xavier, M.D., Karen Sliwa, M.D., Ph.D., Antonio Dans, M.D., Alvaro Avezum, M.D., Ph.D., Leopoldo S. Piegas, M.D., Ph.D., Katalin Keltai, M.D., Ph.D., Matyas Keltai, M.D., Ph.D., Irina Chazova, M.D., Ph.D., Ron J.G. Peters, M.D., Ph.D., Claes Held, M.D., Ph.D., Khalid Yusoff, M.D., Basil S. Lewis, M.D., Petr Jansky, M.D., Alexander Parkhomenko, M.D., Ph.D., Kamlesh Khunti, M.D., Ph.D., William D. Toff, M.D., Christopher M. Reid, Ph.D., John Varigos, B.Sc., Lawrence A. Leiter, M.D., Dora I. Molina, M.D., Robert McKelvie, M.D., Ph.D., Janice Pogue, Ph.D.,* Joanne Wilkinson, B.A., Hyejung Jung, M.Sc., Gilles Dagenais, M.D., and Salim Yusuf, M.B., B.S., D.Phil., for the HOPE-3 Investigators†

ABSTRACT

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.

HOPE 3 Population

- Male age >/ 55 yr, female age >/= 65 yrs; mean age 65.7 yrs; CVD exclusion
- Additional CVD risk factor: tobacco, dysglycemia, fhx premature CAD, mild renal dysfunction
- Mean entry BP 138/82
- Symptomatic hypotension 3.4% vs 2.0%, p < 0.001 in active treatment group

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HOPE 3

- Sponsorship: Canadian Institutes of Health Research
- N = 12,705 Duration 5.6 yrs
- Randomized to candesartan 16 mg + HCTZ 12.5 mg vs placebo
- Active treatment reduced BP 6/3 mmHg vs placebo
- No Difference in primary endpoint: combination of fatal/nonfatal MI + fatal/nonfatal stroke

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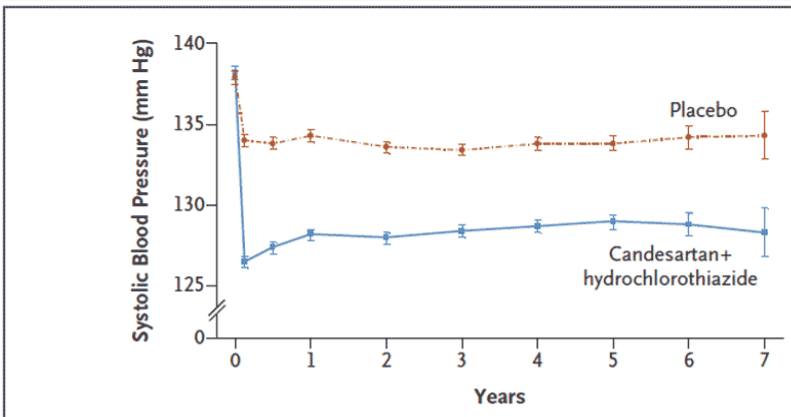


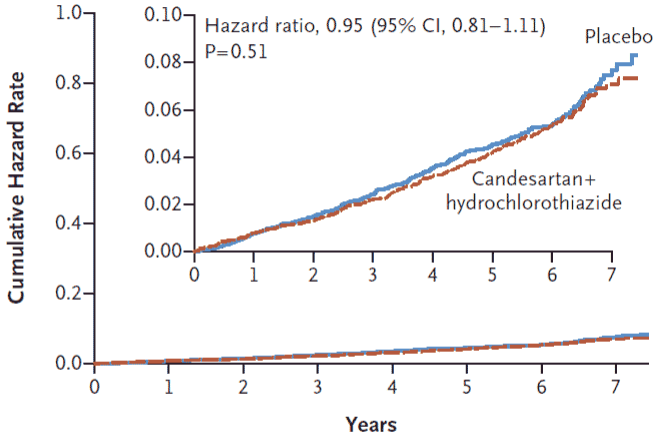
No. at Risk

Candesartan+hydrochlorothiazide	6356	5907	5667	5446	5213	3862	1437	350
Placebo	6347	5879	5623	5442	5186	3822	1424	334

Figure 1. Systolic Blood Pressure over the Course of the Trial, According to Trial Group.

I bars represent 95% confidence intervals.

A Death from Cardiovascular Causes, Myocardial Infarction, Stroke, Cardiac Arrest, Revascularization, or Heart Failure



No. at Risk

Candesartan+hydrochlorothiazide	6356	6272	6200	6103	5968	4969	2076	522
Placebo	6349	6270	6198	6096	5967	4970	2075	488

HOPE – 3 Was a Low Risk Population

- Observed CVD events over 5.6 years was 5%
- Prespecified HOPE 3 subgroup in upper tertile of SBP, >/=143.5 mmHg, placebo group observed CVD events over 5.6 yrs was 6.5%, and this group had a significant 27% CVD event reduction with treatment

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Historical Comparison of ARRs and CVD event rates

- VAH 1970 (DBP 90-114 mmHg): 18% vs 4.8%
- Population studies 1990s (ARIC,CHS): 4%/yr
- ACCORD comparison group 2.1%/yr
- SPRINT comparison group 2.2%/yr
- Cholesterol guideline ARR 2.3%/yr
- HOPE 3 control group 0.8%/yr
- HOPE 3: slight benefit for preselected upper tertile SBP benefit (>143.5) and harm for lower SBP tertile (</= 131.5)

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Systematic Review and Meta-analysis: BP Lowering for prevention of CVD and Death.

- 123 trials, minimum of 1000 patient yrs; 613,815 individuals
- Every 10 mm Hg reduction in SBP reduced major CVD, CAD, stroke, HF
- Supports SBP goal < 130 for individuals with hx CVD, CVA, DM, HF, CKD
- Trials included CVD drug effect trials, ie ACEI benefit for CAD, and surrogate endpoint trials, ie carotid intima/medial thickness

Ettehad D, et al. Lancet 2016

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Systematic Review and Meta-analysis: Association of BP lowering and CVD across BP Levels.

- 74 trials, minimum 1000 patient yrs; 306,273 participants
- Primary prevention of CVD is dependent on baseline SBP
- Baseline SBP >/= 140: sig benefit for mortality and CVD events
- Baseline SBP < 140: no benefit
- Trials included CVD drug effect trials, ie ACEI benefit for CAD, and surrogate endpoint trials ie. carotid intima/media thickness

Brunstrom M, Carlberg B. JAMA Int Med; 2018

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BP Lowering Treatment Trialist's Collaboration: a Meta-analysis of Individual Patient Data Lancet vol 384; 2014

- 11 trials with minimum 1000 patient yrs; 67,475 individuals
- Endpoints: fatal and nonfatal stroke, fatal and nonfatal CAD
- 4 risk groups defined based on age, sex, SBP, DBP, DM, smoking, hx CVD (not lipids due to lack of data)
- RRR of 18% reduction with BP treatment for each risk group
- ARR per 1000 pts x 5 yrs: 14 events, 20, 24, and 38
- BP Trialists analysis based on achieved BPs rather than intention to treat BPs

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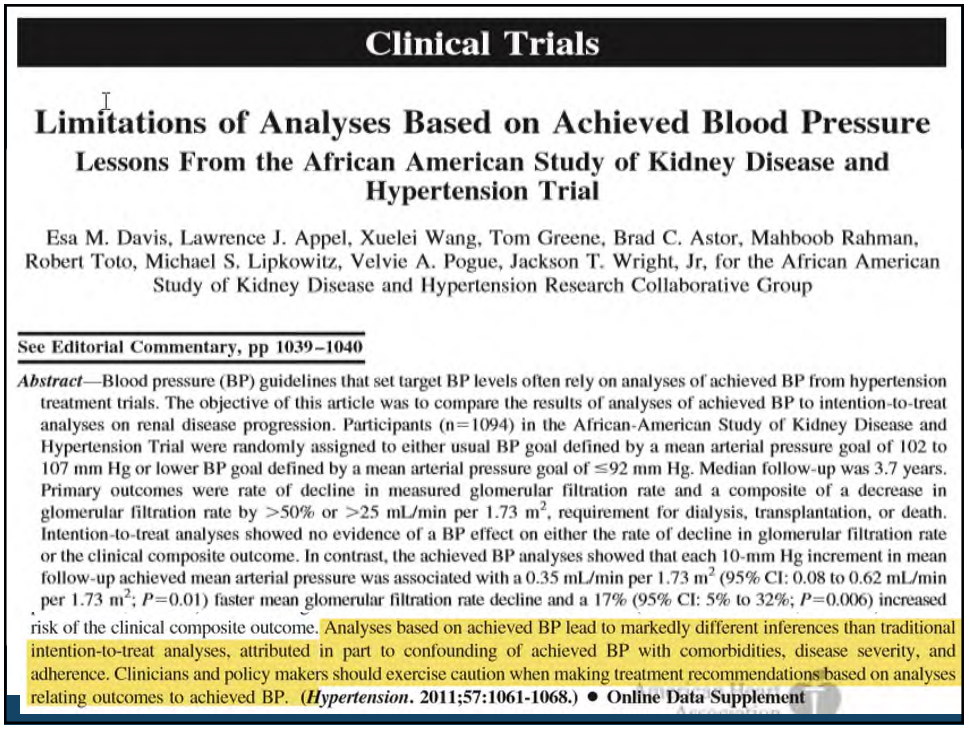

Clinical Trials

Limitations of Analyses Based on Achieved Blood Pressure

Lessons From the African American Study of Kidney Disease and Hypertension Trial

Esa M. Davis, Lawrence J. Appel, Xuelei Wang, Tom Greene, Brad C. Astor, Mahboob Rahman, Robert Toto, Michael S. Lipkowitz, Velvie A. Pogue, Jackson T. Wright, Jr, for the African American Study of Kidney Disease and Hypertension Research Collaborative Group

See Editorial Commentary, pp 1039–1040

Abstract—Blood pressure (BP) guidelines that set target BP levels often rely on analyses of achieved BP from hypertension treatment trials. The objective of this article was to compare the results of analyses of achieved BP to intention-to-treat analyses on renal disease progression. Participants (n=1094) in the African-American Study of Kidney Disease and Hypertension Trial were randomly assigned to either usual BP goal defined by a mean arterial pressure goal of 102 to 107 mm Hg or lower BP goal defined by a mean arterial pressure goal of ≤92 mm Hg. Median follow-up was 3.7 years. Primary outcomes were rate of decline in measured glomerular filtration rate and a composite of a decrease in glomerular filtration rate by >50% or >25 mL/min per 1.73 m^2, requirement for dialysis, transplantation, or death. Intention-to-treat analyses showed no evidence of a BP effect on either the rate of decline in glomerular filtration rate or the clinical composite outcome. In contrast, the achieved BP analyses showed that each 10-mm Hg increment in mean follow-up achieved mean arterial pressure was associated with a 0.35 mL/min per 1.73 m^2 (95% CI: 0.08 to 0.62 mL/min per 1.73 m^2; P=0.01) faster mean glomerular filtration rate decline and a 17% (95% CI: 5% to 32%; P=0.006) increased risk of the clinical composite outcome. Analyses based on achieved BP lead to markedly different inferences than traditional intention-to-treat analyses, attributed in part to confounding of achieved BP with comorbidities, disease severity, and adherence. Clinicians and policy makers should exercise caution when making treatment recommendations based on analyses relating outcomes to achieved BP. (*Hypertension*. 2011;57:1061-1068.) • Online Data Supplement

Why Not Use Achieved Blood Pressures?

- Mean achieved BPs are not Goal BPs
- Post Hoc Analyses of patients achieving lower BPs tend to identify those at lower risk: less LVH, lower baseline BPs, fewer meds, improved med adherence

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Cochrane Database of Systematic Reviews: Treatment Blood Pressure Targets for Hypertension 2009

"The cohort of patients with low blood pressure as identified by achieved blood pressure selects for patients who did not have sustained elevated blood pressure in the first place, for patients in whom the blood pressure is most easily reduced, for patients with the lowest baseline blood pressure, and for patients who are most compliant (healthy user effect, Dormuth 2009)."

continued …

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Cochrane 2009 continued

"All of these factors are most likely associated with a lower risk of having an adverse cardiovascular event. The approach is thus heavily biased for finding less cardiovascular events in the patients with lower blood pressure."

Arguedas JA, Perez MI, Wright JM

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Summary

- Randomized controlled goal blood pressure trials represent the gold standard for deciding guideline goal BP standards
- Meta-analyses contain significant bias as a result of trial inclusions and use of achieved rather than intention to treat BPs, and as a result have reached disparate conclusions
- SPRINT is an NIH supported hypertension trial of major significance, comparable to VAH, SHEP, and ALLHAT
- SBP measurement in SPRINT may represent a 10-20 mmHg difference vs standard BP measurement
- Generalizability of SPRINT results apply to 7.6% U.S. adults and 16.7% of U.S. adults with hypertension (Bress AP, JACC 2016)

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ACP/AAFP Hypertension Guideline 2017

- Age >/= 60 goal SBP < 150 mmHg (strong)
- Age >/= 60, hx CVA/TIA consider goal SBP < 140 mmHg to reduce recurrent stroke (weak)
- Age 60 and over at high CVD risk, consider goal SBP < 140 (weak)

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ACP/AAFP Guideline Critique

- Prespecified SPRINT subgroup age >/75 had significant mortality and CVD event benefit for a SBP goal < 130-140 mmHg by usual measure
- Difficult to justify goal SBP < 150 without CVD for age 60-74 when consensus SBP goal <140 for age 18-59 in all guidelines

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ACC/AHA Hypertension Guideline 2017

- "Use of BP-lowering medication is recommended for secondary prevention of recurrent CVD events…and primary prevention for an estimated 10 yr ASCVD score >/= 10%...for BP >/= 130/80" grade 1 [SPRINT criterion was score >/= 15%]
- "Use of BP-lowering medication is recommended for primary prevention for an estimated 10 yr ASCVD score < 10%..for BP >/= 140/90" grade 1 page 71

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ACC/AHA Hypertension Guideline 2017

- "For adults with confirmed hypertension without additional markers for increased CVD risk, a BP target <130/80 may be reasonable" (IIb) page 83
- Stroke goal < 140/90, <130/80 "may be reasonable"
- DM goal <130/80 grade 1 evidence

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ACC/AHA Guideline Critique

- JNC 8 DBP goal < 90 mmHg is based on 5 high quality DBP trials (HDFP, HTN-Stroke Cooperative, MRC, ANBP, VA Cooperative)
- HOT is only RCT to address DBP 90 vs 80, finding no difference
- ACCORD for DM found no difference SBP 130 mmHg vs 150 mmHg [ADA goal is < 140/90]
- SPRINT eligibility for ~ 20% of adults treated for hypertension and ~ 10% total adults in U.S.

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Hypertension Guidelines 2018

- Competing guidelines from AHA/ACC, ACP/AAFP, and ADA have created confusion
- Randomized controlled trials such as SPRINT represent gold standard goalposts; systematic reviews and meta-analyses contain inherent bias
- 99% of hypertension patients are treated by primary care physicians
- ACC/AHA guideline group did not contain representation from major primary care professional societies

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Competitive Eating Contest Question

Which of the following contests recorded the highest sodium ingestion in 2018?

A. Bratworst

B. Bacon

C. Hot dogs

D. Pizza

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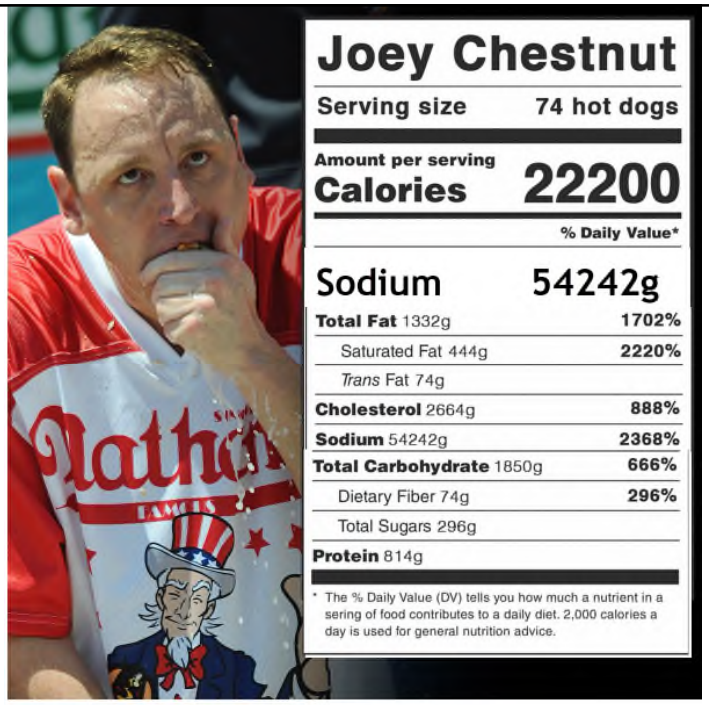


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