Blood Pressure Control in Older Persons and Other Special Populations: How Low Should We Go ?

November 9, 2018
Orange County Symposium on CVD Prevention

Jeff Brettler, MD, SCAL Kaiser HTN Lead

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Agenda

- Measurement issues
- Guideline and Evidence Review
- Older patients
- Diabetes
- CKD

NOTHING TO DISCLOSE

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Patient Case

80 year old woman with repeat BP 154/82 on amlodipine 5 mg daily. Home BPs run 140-150 SBP. She has normal cognition but considers herself somewhat frail (difficulty with some household duties, climbing a few flights of stairs). Community dweller; 10 year CVD risk of 24%.

Her goal BP is:

- < 150/90
- < 140/90
- < 130/90
- < 130/80

Question # 2 – same patient

Intensive (vs standard) treatment can expect to lead to following outcomes:

- Increased falls
- Increased renal failure
- Increased electrolyte disorders
- Increased orthostasis

Question # 3 – same patient

In further discussion with this patient, she wants to know possible benefits of intensive BP treatment. Which of following are possible benefits:

- Decrease in incidence of CV events and/or mortality
- Decrease in dementia
- Decrease in mild cognitive impairment
- Some combination of above

Significance of HTN

- HTN is quantitatively the most important risk factor for premature CVD, being more common than smoking, dyslipidemia and diabetes.
- HTN accounts for an estimated 54% of all strokes and 47% of all ischemic heart disease events globally. (Lancet 2008; 371; 1513 – Global burden of blood pressure related disease 2001).
- Increases the risk for CKD, HF, afib and PVD.

And treatment works!

Large scale RCTs show that antihypertensive treatment results in the following:

- 50% reduction in heart failure
- 30-40% reduction in stroke
- 20-25% reduction in MI

BMJ 2008: BP Trialists' BP lowering collaboration

What's new since JNC 8

- USPSTF guidelines on how to make a dx of HTN - 2015
- SPRINT – 2015. 75+ 2016, CKD 2017, MIND 2019
- HOPE-3 - 2016
- lots of meta-analyses
- ACP/AAFP guidelines - 2017
- ACC/AHA guidelines - 2017

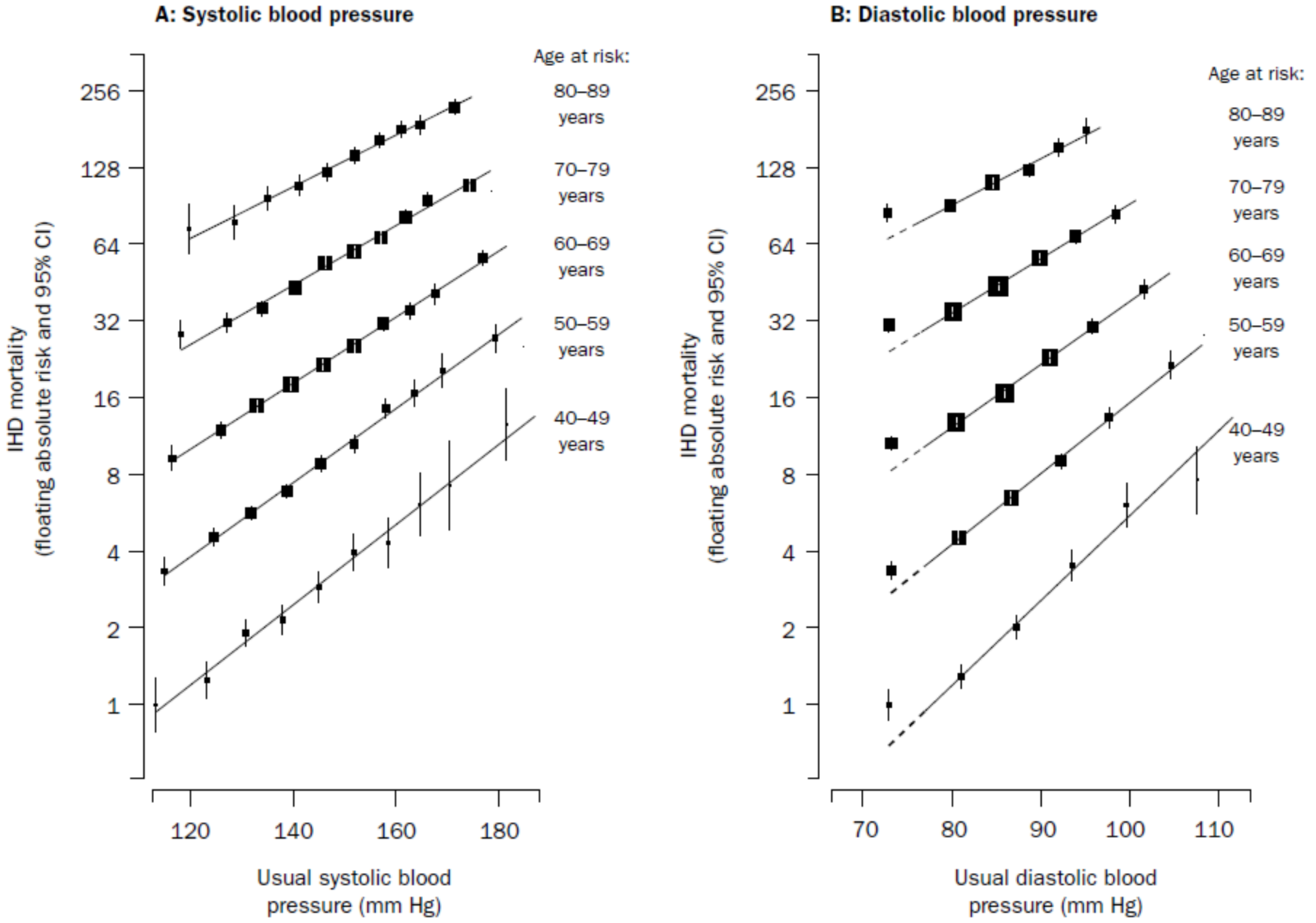
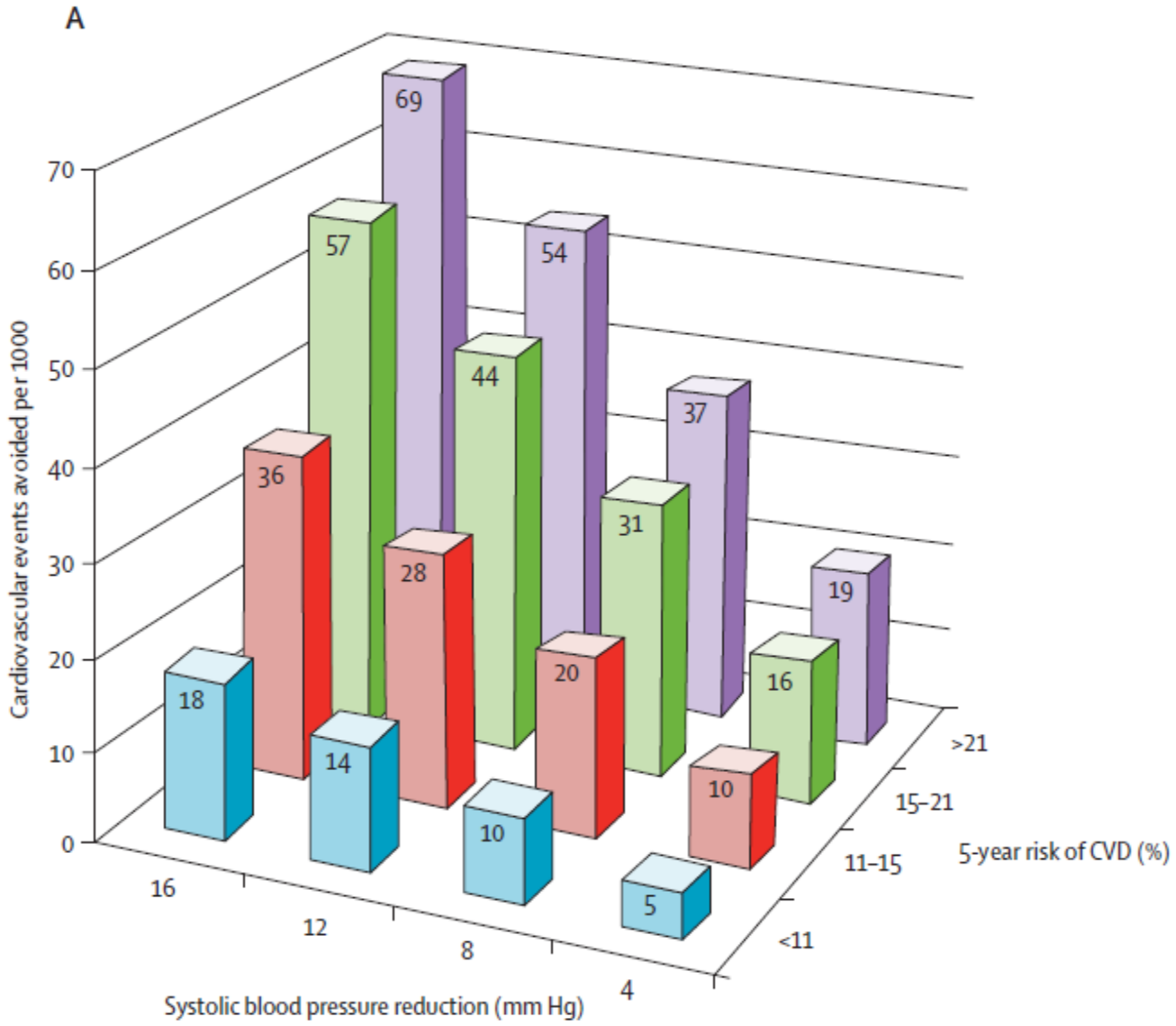


Figure 4: **Ischaemic heart disease (IHD) mortality rate in each decade of age versus usual blood pressure at the start of that decade**
Conventions as in figure 2.



The Blood Pressure Lowering Treatment Trialists' Collaboration – Lancet 2014; 384

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Key Questions

- How do we measure BP?
- How do we define hypertension?
- Systolic goal post SPRINT?
- How is high risk defined?
- Diastolic goal?
- What to do with populations not included in SPRINT?

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US Preventative Service Task Force (USPSTF)

Old Guideline, 2007

Population	Recommendation	Grade
Adults	The USPSTF recommends screening for high BP in adults age 18 years and older.	A

New Guideline, 2015

Population	Recommendation	Grade
Adults 18 and Older	Use office BP as screening test Confirm diagnosis with out of office BP readings prior to initiation of antihypertensive therapy - ABPM is reference standard - Use home BP monitoring when ABPM not available	A

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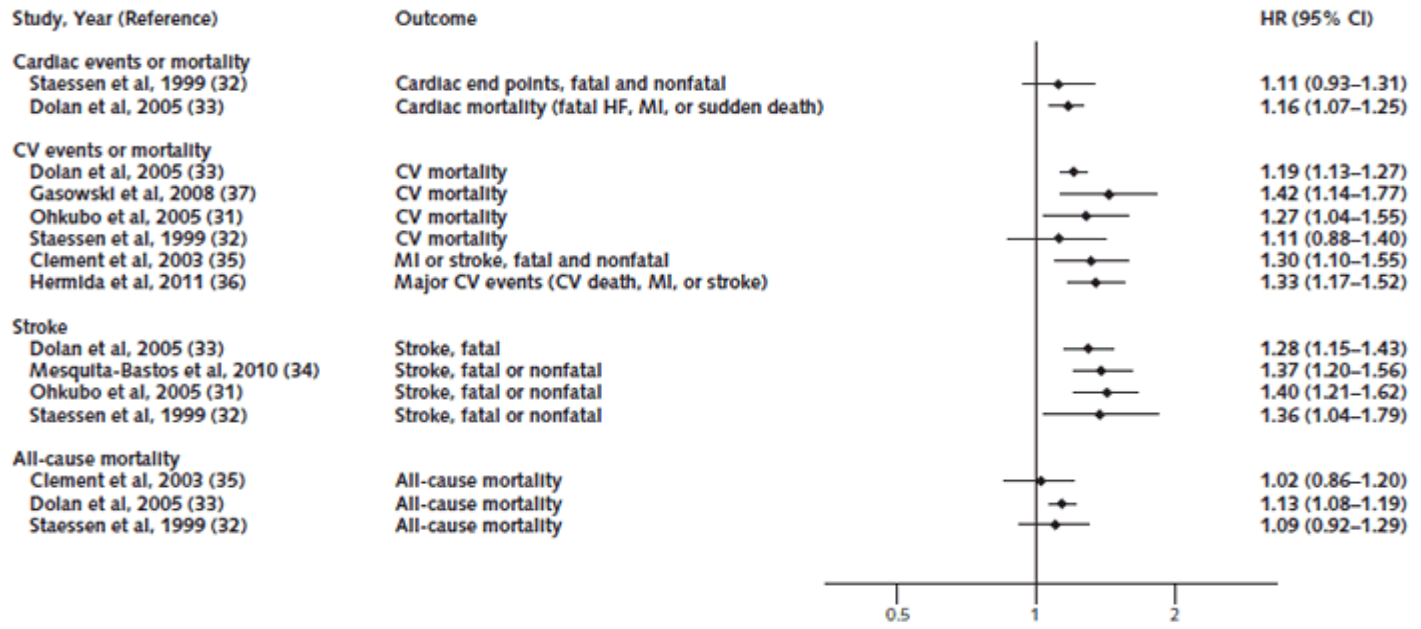
Ambulatory and Home Blood Pressure Monitoring

The USPSTF found that elevated 24-hour ambulatory systolic blood pressure was consistently and significantly associated with stroke and other cardiovascular outcomes, independent of office blood pressure and with greater predictive value. Because of its large evidence base, ABPM is considered the best confirmatory test for hypertension. The USPSTF found 9 studies that evaluated the predictive value of 24-hour ABPM on long-term health outcomes.[1] Four studies found that each 10–mm Hg increment in ambulatory blood pressure (adjusted for office measurements) was significantly associated with increased risk for fatal and nonfatal stroke (Figure 2).[31-34] Six studies found that each 10–mm Hg increment was associated with increased risk for fatal and nonfatal cardiovascular events, with hazard ratios ranging from 1.11 to 1.42 (Figure 2).[31-33, 35-37]

Figure 2. Risk for Cardiovascular Outcomes and Death: 24-h Ambulatory Monitoring of Systolic Blood Pressure, Adjusted for Office Blood Pressure



Weights are from random-effects analysis. CV = cardiovascular; HF = heart failure; HR = hazard ratio; MI = myocardial infarction.

Text Description.

Figure 2 displays a forest plot of the hazard ratios of the risk of cardiovascular outcomes and death among studies that reported 24-hour ambulatory monitoring of systolic blood pressure, adjusted for office blood pressure.

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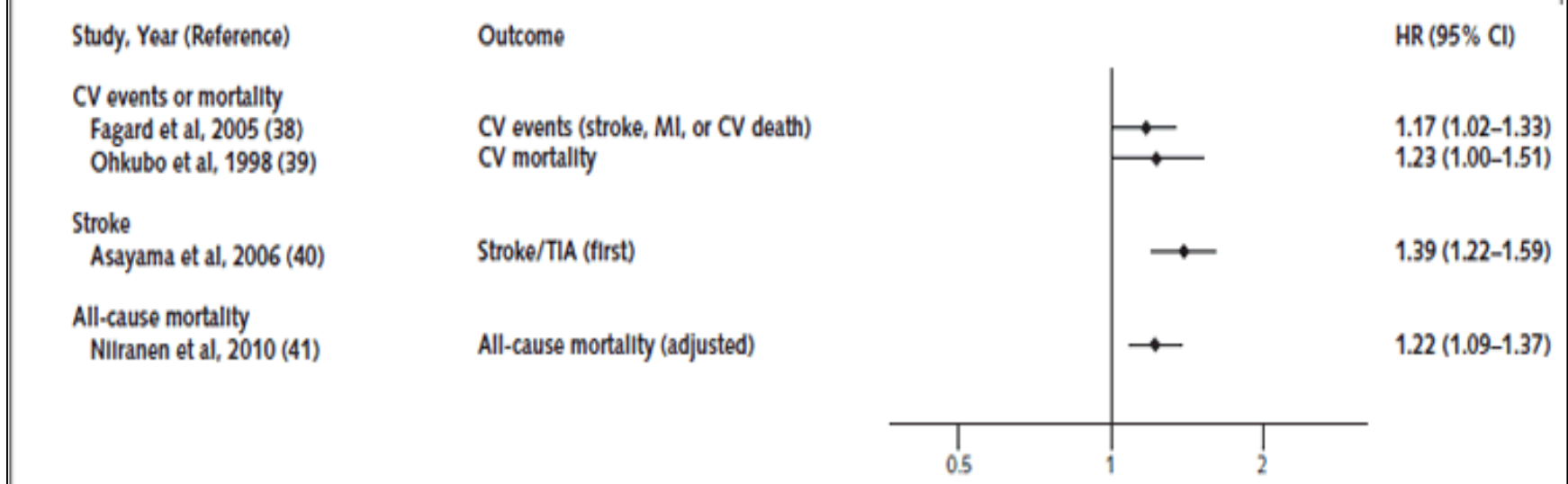
Figure 3. Risk for Cardiovascular Outcomes and Death: Home Monitoring of Systolic Blood Pressure, Adjusted for Office Blood Pressure



Weights are from random-effects analysis. CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; TIA = transient ischemic attack.

Text Description.

Figure 3 displays a forest plot of the hazard ratios of the risk of cardiovascular outcomes and death among studies that reported home monitoring of systolic blood pressure, adjusted for office blood pressure.

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Automated Office Blood Pressure - AOBP

AOBP now recommended as preferred office BP measurement – CHEP 2016

- Automated
- Multiple
- Alone

SPRINT: 5 minute rest, BP measurement, 1 minute rest, BP measurement, 1 minute rest, BP measurement; average of 3 readings

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AOBP Systematic Reviews/Meta-analyses

JAMA IM Feb 2019 – Roerecke et al

- Systolic AOBP: 14.5 mm Hg lower than office, 7.0 mm Hg lower than research
- AOBP = awake ABPM

Hypertension Feb 2019 – Pappaccogli et al

- AOBP 10.5/4.4 lower than MD readings, 6.9/3.8 mm Hg lower than non-MD readings
- AOBP = daytime ABPM; AOBP = home BP

JNC 8 2014

- 60+: goal < 150/90 (Strong recommendation – Grade A)
- < 60: SBP goal < 140 (Expert opinion – Grade E); DBP < 90 (for ages 30-59, strong recommendation – Grade A; for ages 18-29, Expert opinion – Grade E).
- DM: goal < 140/90 (Expert opinion - Grade E)
- CKD: goal < 140/90 (Expert opinion - Grade E)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

ABSTRACT

BACKGROUND

The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

METHODS

We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

RESULTS

At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group. The intervention was stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P<0.001). All-cause mortality was also significantly lower in the intensive-treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90; P=0.003). Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive-treatment group than in the standard-treatment group.

The members of the writing committee (Jackson T. Wright, Jr., M.D., Ph.D., Jeff D. Williamson, M.D., M.H.S., Paul K. Whelton, M.D., Joni K. Snyder, R.N., B.S.N., M.A., Kaycee M. Sink, M.D., M.A.S., Michael V. Rocco, M.D., M.S.C.E., David M. Reboussin, Ph.D., Mahboob Rahman, M.D., Suzanne Oparil, M.D., Cora E. Lewis, M.D., M.S.P.H., Paul L. Kimmel, M.D., Karen C. Johnson, M.D., M.P.H., David C. Goff, Jr., M.D., Ph.D., Lawrence J. Fine, M.D., Dr.P.H., Jeffrey A. Cutler, M.D., M.P.H., William C. Cushman, M.D., Alfred K. Cheung, M.D., and Walter T. Ambrosius, Ph.D.) assume responsibility for the overall content and integrity of the article. The affiliations of the members of the writing group are listed in the Appendix. Address reprint requests to Dr. Wright at the Division of Nephrology and Hypertension, University Hospitals Case Medical Center, Case Western Reserve University, 1100 Euclid Ave. Cleveland, OH 44106-6053, or at jackson.wright@case.edu.

*A complete list of the members of the Systolic Blood Pressure Intervention Trial (SPRINT) Research Group is provided in the Supplementary Appendix, available at NEJM.org.

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
  - Framingham Risk Score for 10-year CVD risk ≥ 15%
  - Age ≥ 75 years

At least one

SPRINT

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

SPRINT

Primary Outcome and Primary Hypothesis

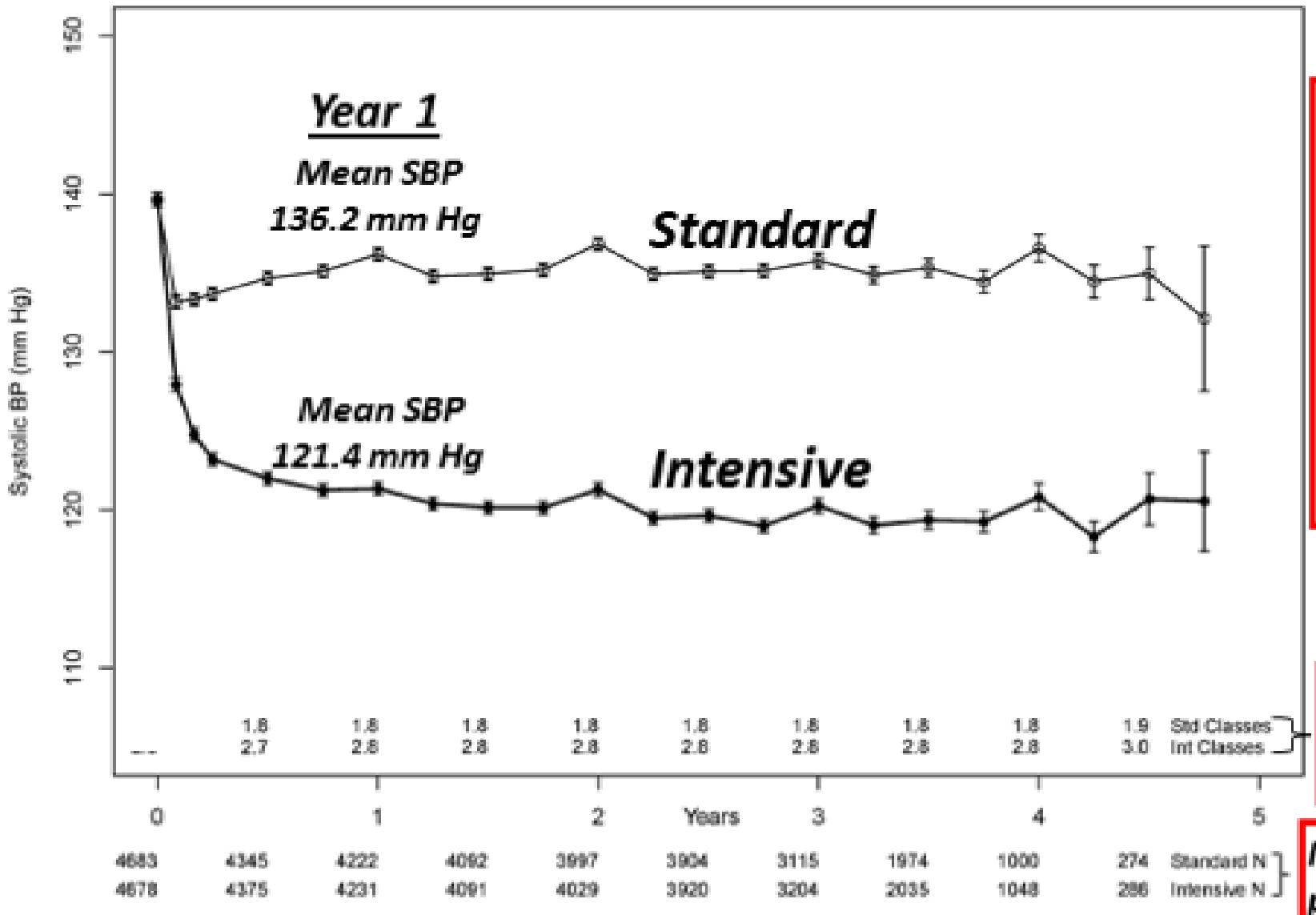
- **Primary outcome**
  - CVD composite: first occurrence of
    - Myocardial infarction (MI)
    - Acute coronary syndrome (non-MI ACS)
    - Stroke
    - Acute decompensated heart failure (HF)
    - Cardiovascular disease death

- **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.

SPRINT

Systolic BP During Follow-up



Average SBP
(During Follow-up)

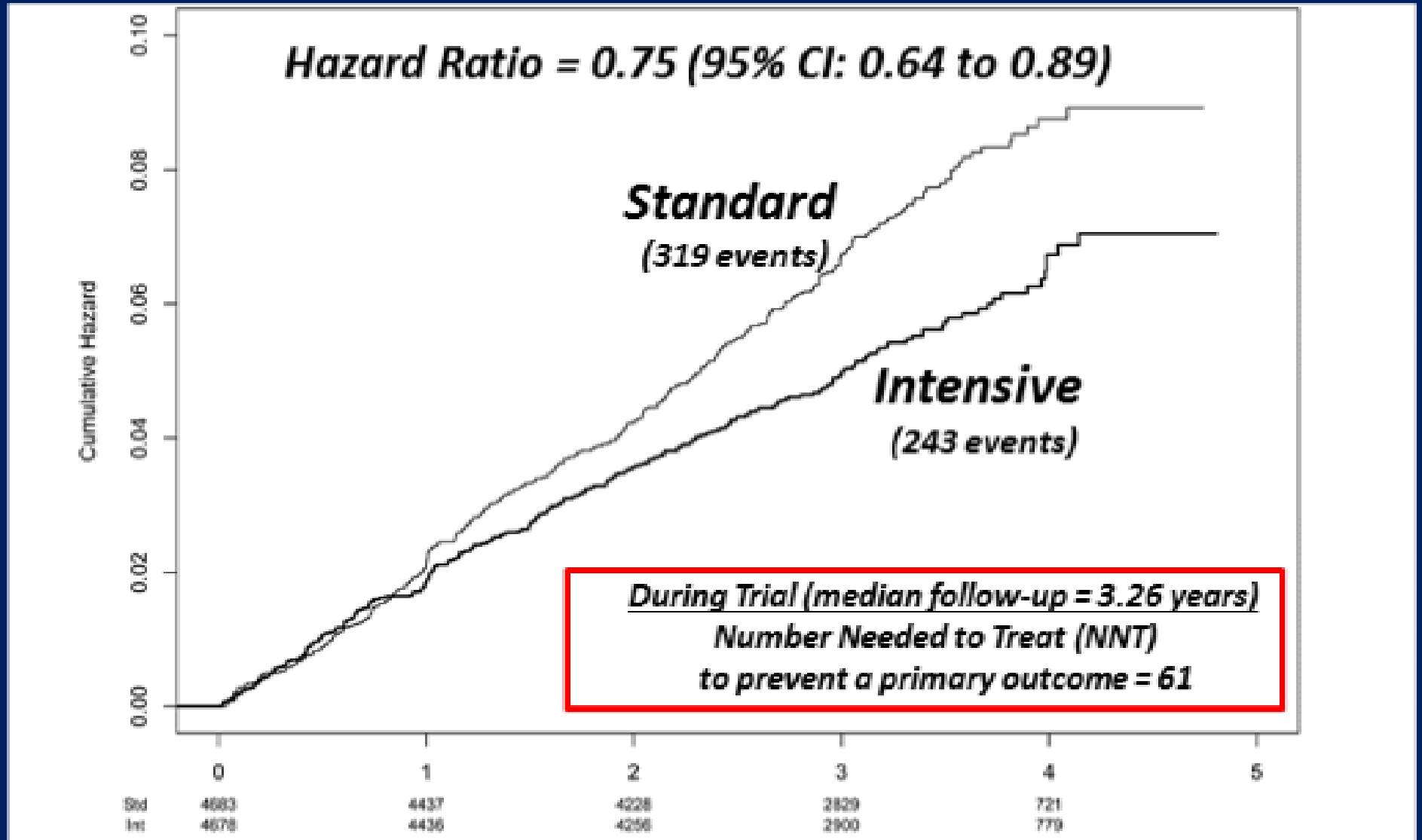
Standard: 134.6 mm Hg

Intensive: 121.5 mm Hg

Average number of antihypertensive medications

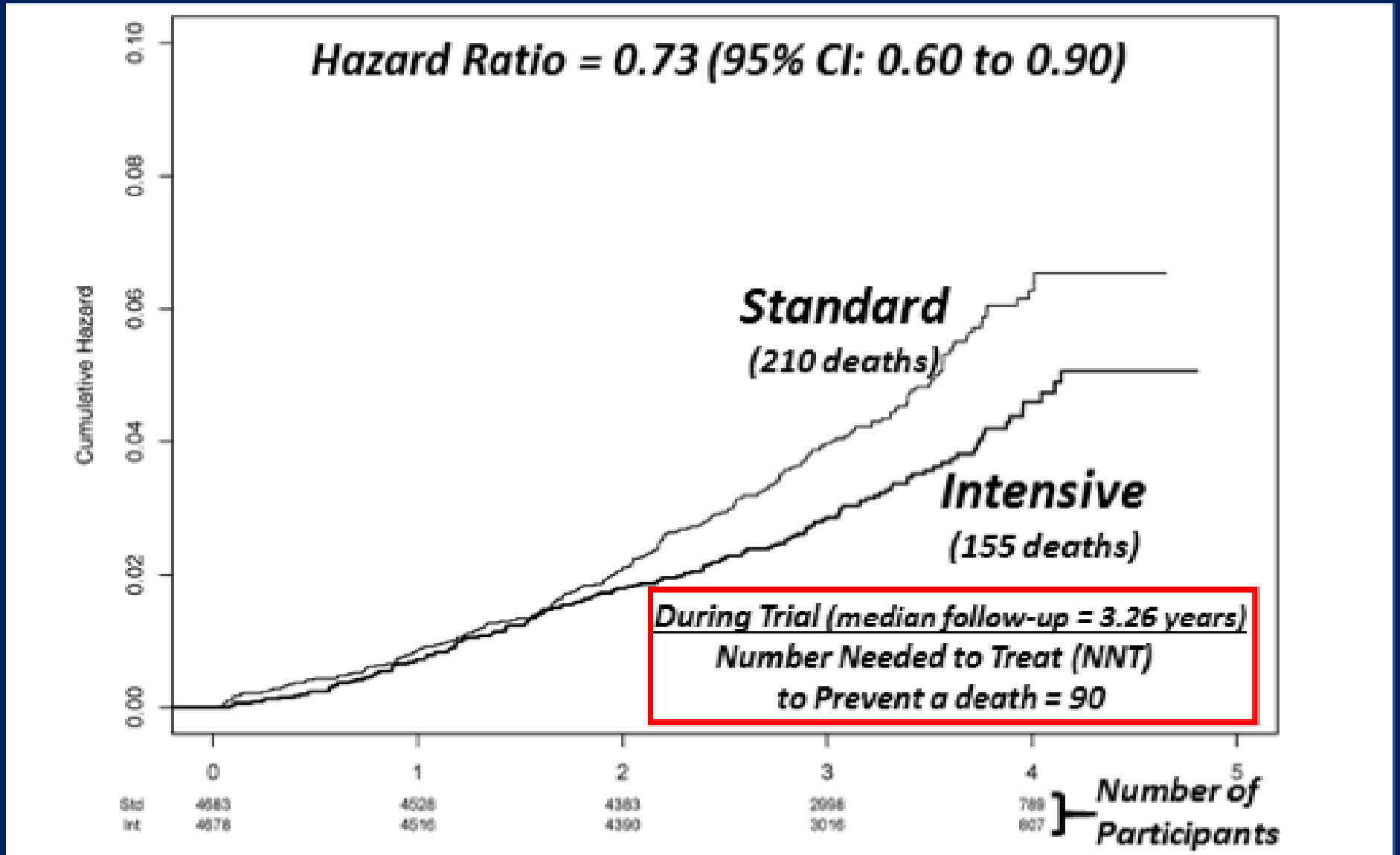
Number of participants

SPRINT Primary Outcome
Cumulative Hazard



Wright JT Jr et al. NEJM 2015; 373: 2103-2116

All-cause Mortality
Cumulative Hazard



SPRINT

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.

SPRINT

SPRINT

Number (%) of Participants with a Monitored Clinical Measure During Follow-up

	Number (%) of Participants		
	Intensive	Standard	HR (P Value)
Laboratory Measures[1]			
Sodium <130 mmol/L	180 (3.9)	100 (2.2)	1.76 (<0.001)
Potassium <3.0 mmol/L	114 (2.5)	74 (1.6)	1.50 (0.006)
Potassium >5.5 mmol/l	176 (3.8)	171 (3.7)	1.00 (0.97)
Signs and Symptoms			
Orthostatic hypotension[2]	777 (16.6)	857 (18.3)	0.88 (0.013)
Orthostatic hypotension with dizziness	62 (1.3)	71 (1.5)	0.85 (0.35)

1. Detected on routine or PRN labs; routine labs drawn quarterly for first year, then q 6 months

2. Drop in SBP ≥20 mmHg or DBP ≥10 mmHg 1 minute after standing (measured at 1, 6, and 12 months and yearly thereafter)

HOPE-3 2016

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.

NEJM April 2016

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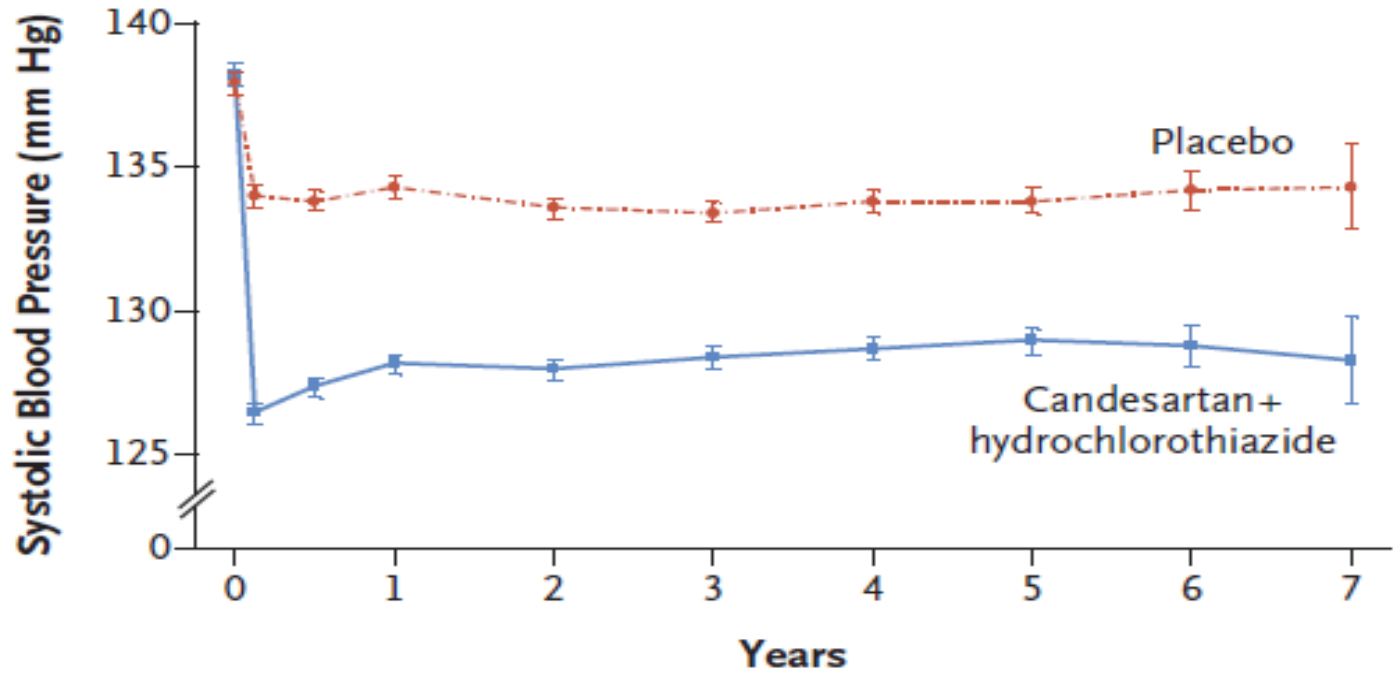
HOPE-3 Trial

- 12,705 participants; mean age 65.7; mean entry BP 138/82
- 5.6 years duration
- Randomized to candesartan 16 mg + HCTZ 12.5 mg vs placebo
- Active treatment – 6/3 mm Hg reduction
- No difference in primary endpoint – combo of fatal/nonfatal MI + fatal/nonfatal stroke
- Symptomatic hypotension slightly increased in treatment group



No. at Risk

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

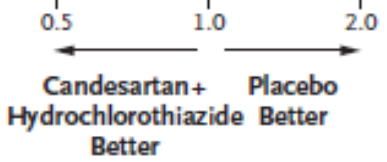
Figure 1. Systolic Blood Pressure over the Course of the Trial, According to Trial Group.

I bars represent 95% confidence intervals.

Lonn et al, NEJM May 2016

A First Coprimary Outcome

Subgroup	Mean Systolic Blood Pressure	Difference in Blood Pressure	Candesartan+ Hydrochlorothiazide	Placebo	Hazard Ratio (95% CI)	P Value for Trend
	mm Hg		*no. of events/total no. of participants (%)*			
Overall	138.1	6.0/3.0	260/6356 (4.1)	279/6349 (4.4)	0.93 (0.79–1.10)	—
Systolic blood pressure						0.02
≤131.5 mm Hg	122.2	6.1/3.1	70/2080 (3.4)	62/2122 (2.9)	1.16 (0.82–1.63)	
131.6–143.5 mm Hg	137.6	5.6/2.7	87/2120 (4.1)	81/2141 (3.8)	1.08 (0.80–1.46)	
>143.5 mm Hg	154.1	5.8/3.0	103/2156 (4.8)	136/2084 (6.5)	0.73 (0.56–0.94)	



B Second Coprimary Outcome

Subgroup	Mean Systolic Blood Pressure	Difference in Blood Pressure	Candesartan+ Hydrochlorothiazide	Placebo	Hazard Ratio (95% CI)	P Value for Trend
	mm Hg		*no. of events/total no. of participants (%)*			
Overall	138.1	6.0/3.0	312/6356 (4.9)	328/6349 (5.2)	0.95 (0.81–1.11)	—
Systolic blood pressure						0.009
≤131.5 mm Hg	122.2	6.1/3.1	90/2080 (4.3)	74/2122 (3.5)	1.25 (0.92–1.70)	
131.6–143.5 mm Hg	137.6	5.6/2.7	99/2120 (4.7)	98/2141 (4.6)	1.02 (0.77–1.34)	
>143.5 mm Hg	154.1	5.8/3.0	123/2156 (5.7)	156/2084 (7.5)	0.76 (0.60–0.96)	

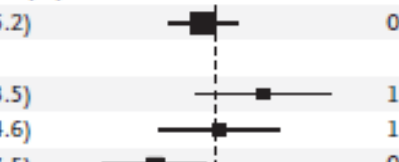


Figure 3. Forest Plots, According to Subgroup of Systolic Blood Pressure for the Coprimary Outcomes.

The difference in blood pressure refers to the average difference of the systolic and diastolic blood pressures between the two groups during the trial, with the active-treatment group having lower mean values. The first coprimary outcome (Panel A) was the composite of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke; the second coprimary outcome (Panel B) was the composite of these events plus resuscitated cardiac arrest, heart failure, or revascularization. Measurements of the systolic blood pressure at baseline were missing for two participants in the placebo group. The size of each square is proportional to the number of events.

Lonn NEJM May 2016

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ACP/AAFP – 60+. Annals of IM March 2017

21 RCTs comparing BP targets or treatment intensity, and 3 observational studies that assessed harms.

- Recommendation 1: target SBP < 150 mm Hg in adults aged 60 years or older (strong rec, high-quality evidence).
- Recommendation 2: consider target SBP < 140 mm Hg in adults aged 60 years or older with a history of stroke or transient ischemic attack (weak rec, moderate-quality evidence).
- Recommendation 3: consider target SBP < 140 mm Hg in some adults aged 60 years or older at high cardiovascular risk, based on individualized assessment* (weak rec, low-quality evidence).

* Vascular disease, most pts with DM, GFR < 45, metabolic syndrome, and older persons.

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2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

AMERICAN COLLEGE of CARDIOLOGY

American Heart Association®
life is why™

ACC/AHA 2017

15 sections, 106 recommendations with following highlights:

- BP measurement
- New BP classification system
- New approach to treatment decisions for management of HTN
- **Lower targets for BP during treatment of HTN**
- Strategies to improve BP control during treatment of HTN

BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.

Table 2.9. Relative risk of all-cause mortality in the intensive [lower] versus the standard [higher] blood pressure group.

Comparison Groups Intensive (lower) vs standard (higher) BP target	Study	Author, Journal (Year)	N	Events, N (%)		RR (95% CI)
				Intensive BP target	Standard BP target	
SBP Target (mm Hg)						
<120 vs <140	ACCORD [28]	Cushman WC, N Engl J Med (2010)	4,733	150 (6.4)	144 (6.1)	1.05 (0.84, 1.30)
<120 vs <140	SPRINT[30]	Wright JT, NEJM (2015)	9,361	155 (3.3)	210 (4.5)	0.74 (0.60, 0.91)
<130 vs <140	Cardio-Sis (31)	Verdecchia P, Lancet (2009)	1,111	4 (0.7)	5 (0.9)	0.79 (0.21, 2.94)
<130 vs 130-149	SPS3 [32]	Benavente, Lancet (2013)	3,020	106 (7.1)	101 (6.6)	1.06 (0.82, 1.38)
<140 vs ≥140 to <150	VALISH [33]	Ogihara T, Hypertension (2010)	3,260	24 (1.6)	30 (2.0)	0.79 (0.47, 1.35)
<140 vs ≥ 140 to <160	JATOS [35]	JATOS, Hypertens Res (2008)	4,418	54 (2.4)	42 (1.9)	1.28 (0.86, 1.91)
SBP/DBP Target (mm Hg)						
95/60-110/75 vs 120/70 – 130/80	HALT-PKD [36]	Schrier RW, NEJM (2014)	480	0 (0.0)	2 (0.7)	0.21 (0.01, 4.30)
<125/<80 vs 125-134/80-84	HOMED-BP [37]	Asayama K, Hypertens Res (2012)	3,518	27 (1.5)	31 (1.8)	0.87 (0.52, 1.45)
<130/80 vs <90	REIN-2 [38]	Ruggenenti P, Lancet (2005)	338	2 (1.2)	3 (1.8)	0.67 (0.11, 3.96)
≤140/90 vs ≤150/90	NR [39]	Wei Y, J Clin Hypertens (2013)	724	51 (14.0)	87 (24.1)	0.58 (0.43, 0.80)
<150/85 vs <180/105	UKPDS [40]	UKPDS Group, BMJ (1998)	1,148	134 (17.7)	83 (21.3)	0.83 (0.65, 1.06)
DBP Target (mm Hg)						
75 vs 80-89	ABCD [41]	Estacio RO, Diabetes Care (2000)	470	13 (5.5)	25 (10.7)	0.51 (0.27, 0.97)
≤80 Hg vs ≤90	HOT [44]	Hansson L, Lancet (1998)	12,528	207 (3.3)	188 (3.0)	1.10 (0.91, 1.34)
MAP Target (mm Hg)						
≤ 92 vs 102-107	AASK [45]	Wright JT Jr., JAMA (2002)	1,094	37 (6.9)	43 (7.8)	0.88 (0.58, 1.35)
≤ 92 vs <107 (age ≤60 y) or < 98 vs <113 (age ≥61 y)	MDRD [47]	Samak MJ, Ann Intern Med (2005)	840	12 (2.8)	7 (1.7)	1.60 (1.00, 2.55)
Meta-analyses	**I^2 (%)**	**Q Test for Heterogeneity**				**RR (95% CI)**
Any SBP target (n=6)	49.21	Q (df = 5) = 9.84, P = 0.08	25,721	493 (3.8)	532 (4.1)	0.95 (0.79, 1.15)
Any SBP/DBP target (n=5)	3.77	Q (df = 4) = 4.16, P = 0.39	6,283	212 (6.7)	203 (7.3)	0.74 (0.61, 0.89)
Intensive SBP target <130 (n= 9)[a]	15.59	Q (df = 8) = 9.48, P = 0.30	24,569	493 (4.0)	546 (4.4)	0.92 (0.79, 1.06)
All studies (n=15)	49.30	Q (df = 14) = 27.61, P = 0.02	46,934	952 (4.0)	1,001 (4.3)	0.89 (0.77, 1.02)
Sensitivity analyses						
100% Diabetic populations (n=3)[b]	60.87	Q (df = 2) = 5.11, P = 0.08	6351	297 (8.8)	252 (3.7)	0.85 (0.64, 1.14)
100% CKD populations (n=3)[c]	0.00	Q (df = 2) = 1.54 , P = 0.46	2269	51 (4.5)	53 (4.7)	0.96 (0.66, 1.40)
Study populations with mean age ≥60y (n=8)[d]	67.11	Q (df = 7) = 21.28 , P = 0.003	38,971	751 (3.9)	807 (4.1)	0.92 (0.76, 1.11)

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ACC/AHA systematic review. Hypertension Nov 2017

ACC-AHA Evidence Review SBP

Table 2.9. Relative risk of all-cause mortality in the intensive [lower] versus the standard [higher] blood pressure group.

Comparison Groups Intensive (lower) vs standard (higher) BP target	Study	Author, Journal (Year)	N	Events, N (%)		RR (95% CI)
				Intensive BP target	Standard BP target	
SBP Target (mm Hg)						
<120 vs <140	ACCORD [28]	Cushman WC, N Engl J Med (2010)	4,733	150 (6.4)	144 (6.1)	1.05 (0.84, 1.30)
<120 vs <140	SPRINT[30]	Wright JT, NEJM (2015)	9,361	155 (3.3)	210 (4.5)	0.74 (0.60, 0.91)
<130 vs <140	Cardio-Sis (31)	Verdecchia P, Lancet (2009)	1,111	4 (0.7)	5 (0.9)	0.79 (0.21, 2.94)
<130 vs 130-149	SPS3 [32]	Benavente, Lancet (2013)	3,020	106 (7.1)	101 (6.6)	1.06 (0.82, 1.38)
<140 vs ≥140 to <150	VALISH [33]	Ogihara T, Hypertension (2010)	3,260	24 (1.6)	30 (2.0)	0.79 (0.47, 1.35)
<140 vs ≥ 140 to <160	JATOS [35]	JATOS, Hypertens Res (2008)	4,418	54 (2.4)	42 (1.9)	1.28 (0.86, 1.91)

ACC-AHA Evidence Review - DBP

Comparison Groups Intensive (lower) vs standard (higher) BP target	Study	Author, Journal (Year)	N	Events, N (%)		RR (95% CI)
				Intensive BP target	Standard BP target	
DBP Target (mm Hg)						
75 vs 80-89	ABCD [41]	Estacio RO, Diabetes Care (2000)	470	13 (5.5)	25 (10.7)	0.51 (0.27, 0.97)
≤80 Hg vs ≤90	HOT [44]	Hansson L, Lancet (1998)	12,528	207 (3.3)	188 (3.0)	1.10 (0.91, 1.34)

JAMA | Original Investigation

March 2019

Levels of Evidence Supporting American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines, 2008-2018

Alexander C. Fanaroff, MD, MHS; Robert M. Califf, MD; Stephan Windecker, MD; Sidney C. Smith Jr, MD; Renato D. Lopes, MD, PhD, MHS

Level of evidence:

- LOE A - multiple RCTs or a single, large RCT
- LOE B - observational studies or a single RCT
- LOE C - expert opinion only

Class:

- 1 – should do
- IIa - should be considered; IIb – may be considered
- III – not recommended

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Level of Evidence Supporting Guidelines

eTable 1. Levels of Evidence by guideline and Category of Recommendation (ACC/AHA Guidelines)

		Overall			Class I			Class II			Class III		
Guideline (N recommendations)	**Year**	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**
High Blood pressure in Adults (n = 116)[2]	2017	21 (18.1)	49 (42.2)	46 (39.7)	17 (25)	26 (38.2)	25 (36.8)	1 (2.4)	20 (48.8)	20 (48.8)	3 (42.9)	3 (42.9)	1 (14.3)

eTable 2. Levels of Evidence by Guideline and Category of Recommendation (ESC Guidelines)

		Overall			Class I			Class II			Class III		
Guideline (N recommendations)	**Year**	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**
General cardiology													
Hypertension (n = 135)[27]	2018	49 (36.3)	39 (28.9)	47 (34.8)	41 (47.1)	18 (20.7)	28 (32.2)	1 (2.9)	19 (54.3)	15 (42.9)	7 (53.8)	2 (15.4)	4 (30.8)

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Age-Related Issues

COR	LOE	Recommendations for Treatment of Hypertension in Older Persons
I	A	Treatment of hypertension with a SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of 130 mm Hg or higher.
IIa	C-EO	For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs.

TABLE 1. Hypertension goals in older adults in recent hypertension guidelines

Guideline	SBP target in mmHg
Less aggressive target beginning at age 80	
Australia (2016) [1]	Age 80+: <150
Brazil (2016) [2]	Age 80+: <150
CHEP (Canada) (2016) [3]	Age 80+: <150
American Society of Hypertension (2014) [4]	Age 80+: <150
International Society of Hypertension (2014) [4]	Age 80+: <150
JNC8 minority (2014) [5]	Age 80+: <150
NICE (2011) [6]	Age 80+: <150
Less aggressive target beginning at age 65±	
European Society (2018) [7]	130–140
Special considerations as to target beginning at age 65±	
ACC/AHA (2017) [8]	Age 65+: community dwelling: <130; others age 65+: individualize
Less aggressive targets beginning at age 60	
American College of Physicians (2017) [9]	Age 60+: <150. Consider <140[a]
American Academy of Family Physicians (2017) [9]	Age 60+: <150. Consider <140[a]
JNC8 (2014) [10]	Age 60+: <150

Roush et al, J of HTN Aug 2019

ACC, American College of Cardiology; AHA, American Heart Association; JNCB, Eighth Joint National Committee; NICE, National Institute for Health and Clinical Excellence.
[a]Consider less than 140 for history of transient ischemic attack or stroke or where there is high cardiovascular risk.

Table 1 Hypertension in older people – treatment outcome studies

Study	Publication and year	Age	Inclusion BP (mmHg)	Average entry BP (mmHg)	Target BP (mmHg)	Mean BP on active treatment (mmHg)	Mean BP on placebo (mmHg)	% reduction in cardiovascular events with active treatment		
								Total CV events	Stroke	CHD events
STOP – 1[13]	Lancet 1991	70–84	SBP ≥ 180 DBP > 90	195/102	< 160/95	167/87	187/95	40	47	13
MRC – 2[15]	BMJ 1992	65–74	SBP 160–209 DBP < 114	185/91	SBP < 150–160	152/78	166/84	17	25	19
SHEP[14]	JAMA 1991	≥ 60	SBP ≥ 160 DBP < 90	170/77	SBP < 160 or D > 20	143/68	155/72	32	36	25
Syst-Eur[16]	Lancet 1997	≥ 60	SBP 160–219 DBP < 95	174/86	SBP < 150 or D > 20	151/79	161/84	31	42	26
HYVET[21]	N Engl J Med 2008	≥ 80	SBP ≥ 160	173/91	< 150/80	143/78	158/84	34	30	28
SPRINT Elderly subgroup[24]	JAMA 2016	≥ 75	SBP 130–180	142/71	Intensive SBP < 120; Standard SBP < 140	123/62 (intensive)	135/67 (standard)	34	28	31

CV = cardiovascular; CHD = coronary heart disease; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; STOP = Swedish Trial in Old Patients; MRC = Medical Research Council; SHEP = Systolic Hypertension in the Elderly Program; BMJ = British Medical Journal; JAMA = Journal of the American Medical Association; D = change; HYVET = Hypertension in the Very Elderly Trial; SPRINT = Systolic Blood Pressure Intervention Trial.

Journal of Pharmacy Practice and Research (2018) 48, 92– 101

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

RESULTS Among 2636 participants (mean age, 79.9 years; 37.9% women), 2510 (95.2%) provided complete follow-up data. At a median follow-up of 3.14 years, there was a significantly lower rate of the primary composite outcome (102 events in the intensive treatment group vs 148 events in the standard treatment group; hazard ratio [HR], 0.66 [95% CI, 0.51-0.85]) and all-cause mortality (73 deaths vs 107 deaths, respectively; HR, 0.67 [95% CI, 0.49-0.91]). The overall rate of serious adverse events was not different between treatment groups (48.4% in the intensive treatment group vs 48.3% in the standard treatment group; HR, 0.99 [95% CI, 0.89-1.11]). Absolute rates of hypotension were 2.4% in the intensive treatment group vs 1.4% in the standard treatment group (HR, 1.71 [95% CI, 0.97-3.09]), 3.0% vs 2.4%, respectively, for syncope (HR, 1.23 [95% CI, 0.76-2.00]), 4.0% vs 2.7% for electrolyte abnormalities (HR, 1.51 [95% CI, 0.99-2.33]), 5.5% vs 4.0% for acute kidney injury (HR, 1.41 [95% CI, 0.98-2.04]), and 4.9% vs 5.5% for injurious falls (HR, 0.91 [95% CI, 0.65-1.29]).

JAMA May 2016

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SPRINT 75+, JAMA MAY 2016

- Primary outcome decreased 34% (p 0.001); mortality decreased 33% (p 0.009)
- NNT 27 for composite outcome, NNT 41 for total mortality (3.14 years); compared with 61/90 for total population
- Absolute rate of hypotension, electrolyte abnormalities, syncope, acute kidney injury higher in intensive, but not significant;
- Injurious falls higher in standard, but not significant
- No difference in orthostatic hypotension and overall adverse effects.
- Frail patients achieved same benefit (vs fit and less-fit).

Table 1. Systolic Blood Pressure Intervention Trial (SPRINT) Exclusion Criteria

- Diabetes mellitus
- Prior stroke
- Dementia diagnosis
- Not receiving disease-appropriate antihypertensive therapy (e.g., beta-blocker after recent myocardial infarction)
- Secondary cause of hypertension
- If able to stand, 1-minute standing systolic blood pressure <110 mmHg
- Proteinuria in any of the following ranges
  - ≥1 g/d urine protein
  - ≥600 mg/d urine albumin
  - Spot protein:creatinine ≥1 g protein/g creatinine
  - Spot albumin:creatinine ≥600 mg/g creatinine
  - Urine dipstick ≥2+ protein if none of the above are available
- Polycystic kidney disease
- Glomerulonephritis
- Estimated glomerular filtration rate <20 mL/min per 1.73 m^2
- Cardiovascular event, procedure, or hospitalization for unstable angina pectoris in prior 3 months
- Symptomatic heart failure in prior 6 months
- Left ventricular ejection fraction <35%
- Unintentional weight loss >10% in prior 6 months
- Life-limiting illness
- Anticipated survival <3 years
- Nursing home residence
- Poor adherence
- Organ transplant

Rich, Ouslander, JAGS 2018

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Generalizability of SPRINT in 75+

- Based on an analysis of data from the 2007 to 2012 National Health and Nutrition Examination Surveys (NHANES), only 34.6% U.S. adults aged 75 and older fulfill SPRINT eligibility criteria.
- Of adults in this age group with treated hypertension, only 31.3% would be eligible for SPRINT.*
- Thus, approximately two-thirds of adults aged 75 and older would have been excluded from SPRINT, and the generalizability of the SPRINT findings to this population is at best uncertain.

*Bress AP, Tanner RM, Hess R, Colantonio LD, Shimbo D, Muntner P. Generalizability of SPRINT results to the U.S. adult population. J Am Coll Cardiol 2016;67:463–72.

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SPRINT MIND

Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

Outcomes	Treatment Group				Hazard Ratio (95% CI)[a]	*P* Value
	Intensive		Standard			
	No. With Outcome/Person-Years	Cases per 1000 Person-Years	No. With Outcome/Person-Years	Cases per 1000 Person-Years		
Probable dementia	149/20 569	7.2	176/20 378	8.6	0.83 (0.67-1.04)	.10
Mild cognitive impairment[b]	287/19 690	14.6	353/19 281	18.3	0.81 (0.69-0.95)	.007
Composite of mild cognitive impairment or probable dementia	402/19 873	20.2	469/19 488	24.1	0.85 (0.74-0.97)	.01

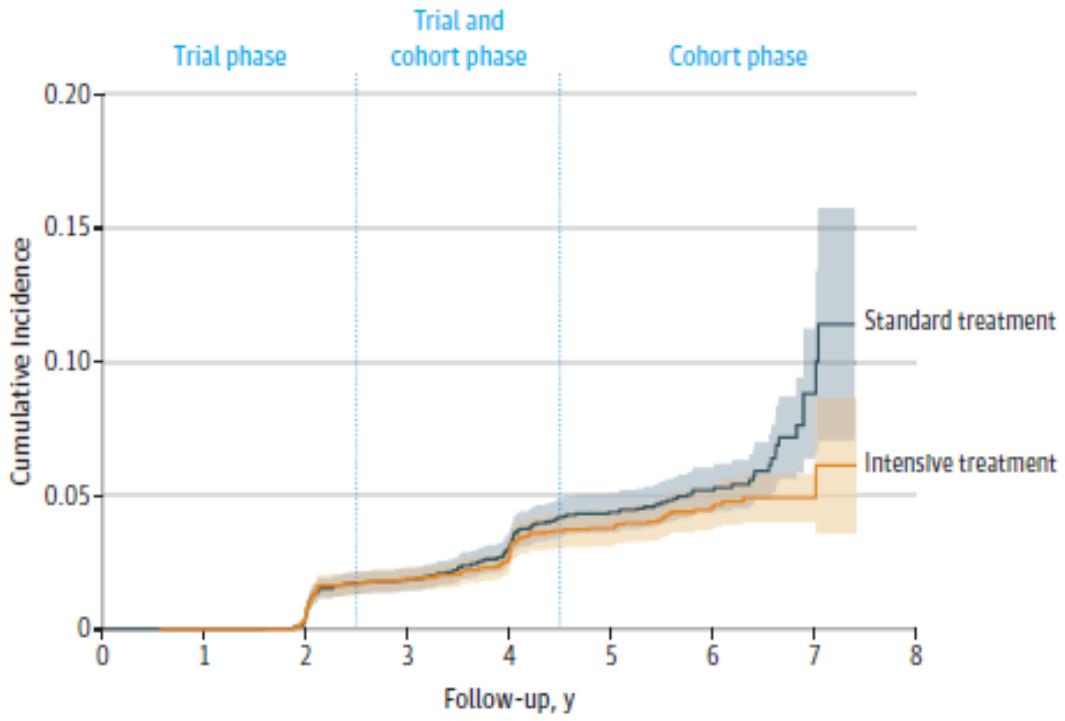
[a] Intensive treatment group vs standard treatment group based on Cox proportional hazards regression.

[b] Participants adjudicated as having probable dementia at the first follow-up visit (year 2) do not contribute to the analyses of mild cognitive impairment.

Williamson et al., JAMA Jan 2019

SPRINT MIND

Figure 2. Probable Dementia by Treatment Group



No. at risk									
Standard treatment	4285	4282	4168	3886	2829	2107	989	87	0
Intensive treatment	4278	4277	4171	3917	2893	2189	1027	93	0

Shaded regions indicate 95% confidence intervals. Median follow-up time was 5.14 years (interquartile range, 3.91-6.00) for the intensive treatment group and 5.07 years (interquartile range, 3.87-5.98) for the standard treatment group. For group comparison of incidence, hazard ratio, 0.83; 95% CI, 0.67-1.04; *P*=.10.

SPRINT MIND Caveats/Conclusions

- The cognitive assessment and dementia adjudication continued for almost 3 years after the SPRINT trial ended as a cohort phase, for a mean total follow-up of almost 6 years.
- Possible larger effect if intervention continued? Mean SBP difference of 13.3 mm during trial, 6.4 mm after (SBP increased to 129.2 in intervention group).
- Adverse events not monitored after intervention phase ended (orthostasis, syncope, electrolyte and renal issues). Need this info to balance benefit effect.
- No negative cognitive findings (prior concern over cerebral hypoperfusion).

SPRINT MRI

Table 2. Estimated Changes in Structural Magnetic Resonance Imaging Outcomes by Treatment Group[a]

Outcome	Volume (95% CI), cm^3						Estimated Difference in Change	*P* Value
	Intensive Treatment			Standard Treatment				
	Baseline	Follow-up	Change	Baseline	Follow-up	Change		
WML volume, asinh	1.99 (1.86 to 2.13)	2.14 (2.01 to 2.28)	0.15 (0.11 to 0.19)	1.96 (1.82 to 2.10)	2.25 (2.10 to 2.39)	0.28 (0.24 to 0.33)	−0.13 (−0.19 to −0.07)	<.001
WML volume	4.57 (4.00 to 5.14)	5.49 (4.91 to 6.07)	0.92 (0.69 to 1.14)	4.40 (3.80 to 5.00)	5.85 (5.23 to 6.47)	1.45 (1.21 to 1.70)	−0.54 (−0.87 to −0.20)	
Annualized change			0.23 (0.17 to 0.29)			0.37 (0.30 to 0.43)		
Total brain volume	1134.5 (1125.1 to 1144.0)	1104.0 (1094.5 to 1113.4)	−30.6 (−32.3 to −28.8)	1134.0 (1124.4 to 1143.6)	1107.1 (1097.4 to 1116.8)	−26.9 (−28.8 to −24.9)	−3.7 (−6.3 to −1.1)	.006
Annualized change			−7.7 (−8.1 to −7.3)			−6.8 (−7.3 to −6.3)		

Abbreviations: WML, white matter lesion; asinh, inverse hyperbolic sine transformation, $f(x) = \log(x + (x^2 + 1)^{0.5})$.

[a] Estimates based on a linear mixed model, adjusting for intracranial volume and days since randomization, with random effects for participant and magnetic resonance imaging facility. All estimates computed using the baseline mean intracranial volume of 1382.03 cm^3, with follow-up estimates computed at 1452 days (3.98 years) after randomization. For change estimates, negative values denote decreases from baseline; positive values, increases from baseline. Difference in change represents intensive treatment group minus standard treatment group.

JAMA Aug 2019

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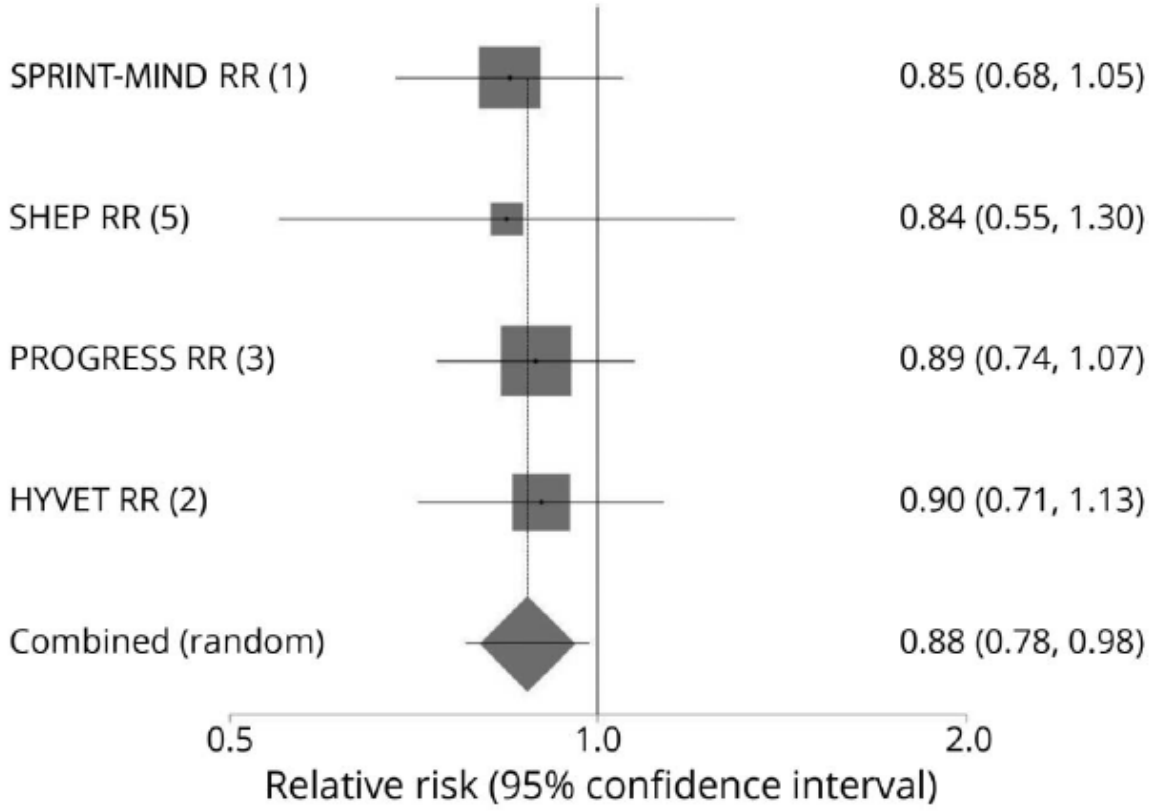
Peters Meta-Analysis – Neurology May 2019

- Including SPRINT MIND, there are now 8 RCTs with dementia outcomes.
- No one trial shows clear treatment benefit, but collective data “more persuasive.”
- Trials were designed for CV outcomes, and generally just a few years of f/u.
- Baseline SBP level varied; difference in achieved SBP 2 to 17 mm. In this analysis, trials with larger separation showed bigger benefit.
- Rates of dementia low and complicated by early CV death and comorbidity.
- Author’s conclusion: SBP lowering of 10 mm lowers risk of dementia (moderately strong evidence).

Figure Meta-analysis of trials of blood pressure (BP)–lowering on dementia outcomes, according to having ≥10 mm Hg systolic BP difference between randomized groups



HYVET = Hypertension in the Very Elderly Trial; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; SHEP = Systolic Hypertension in the Elderly Program; SPRINT-MIND = Systolic Blood Pressure Intervention Trial—Memory and Cognition in Decreased Hypertension.

Peters, et al. Neurology, May 2019;92:1017-1018

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Diabetes Mellitus

COR	LOE	Recommendations for Treatment of Hypertension in Patients With DM
I	SBP: B-R[SR] DBP: C-EO	In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher with a treatment goal of less than 130/80 mm Hg.
I	A[SR]	In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective.
IIb	B-NR	In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria.

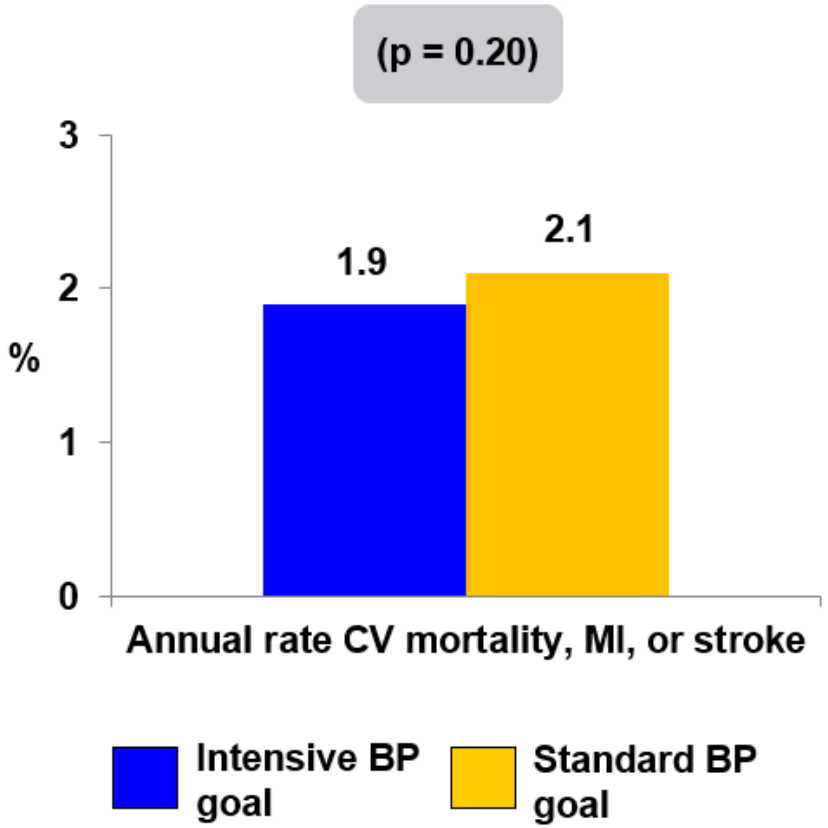
SR indicates systematic review.

ACC-AHA comments on BP goals in DM

- **There is limited quality evidence to determine a precise BP target in adults with DM.** No RCTs have explicitly 1) documented whether treatment to an SBP goal <140 mm Hg versus a higher goal improves clinical outcomes in adults with hypertension and DM or 2) directly evaluated clinical outcomes associated with SBP <130 mm Hg (2). However, 2 high-quality systematic reviews of RCTs support an SBP target of <140 mm Hg (4, 7).
- **There is little or no available RCT evidence supporting a specific DBP threshold for initiation of pharmacological therapy**. Several RCTs, including the HOT (Hypertension Optimal Treatment) trial, UKPDS (United Kingdom Prospective Diabetes Study), and ABCD (Appropriate Blood Pressure Control in Diabetes) trial (19-22), are often cited to support a lower DBP target (e.g., ≤85 or 80 mm Hg) for adults with hypertension and DM. However, these trials were conducted when the diagnostic criteria for DM were more conservative than they are currently (2 fasting glucose levels >140 mg/dL as opposed to 126 mm/dL today).

ACCORD BP

Trial design: Half of the diabetic patients within the main ACCORD trial were randomized to a goal systolic blood pressure (BP) <120 mm Hg (n = 2,362) vs. <140 mm Hg (n = 2,371).



www.cardiosource.org

Results

- Mean systolic BP at 1 year was 119 mm Hg in the intensive group vs. 134 mm Hg in the standard group
- Mean number of antihypertensives was 3.4 vs. 2.1, respectively
- Annual rate of cardiovascular mortality, myocardial infarction, or stroke was 1.9% vs. 2.1% (p = 0.20)
- Serious adverse events were 3.3% vs. 1.3% (p < 0.001)

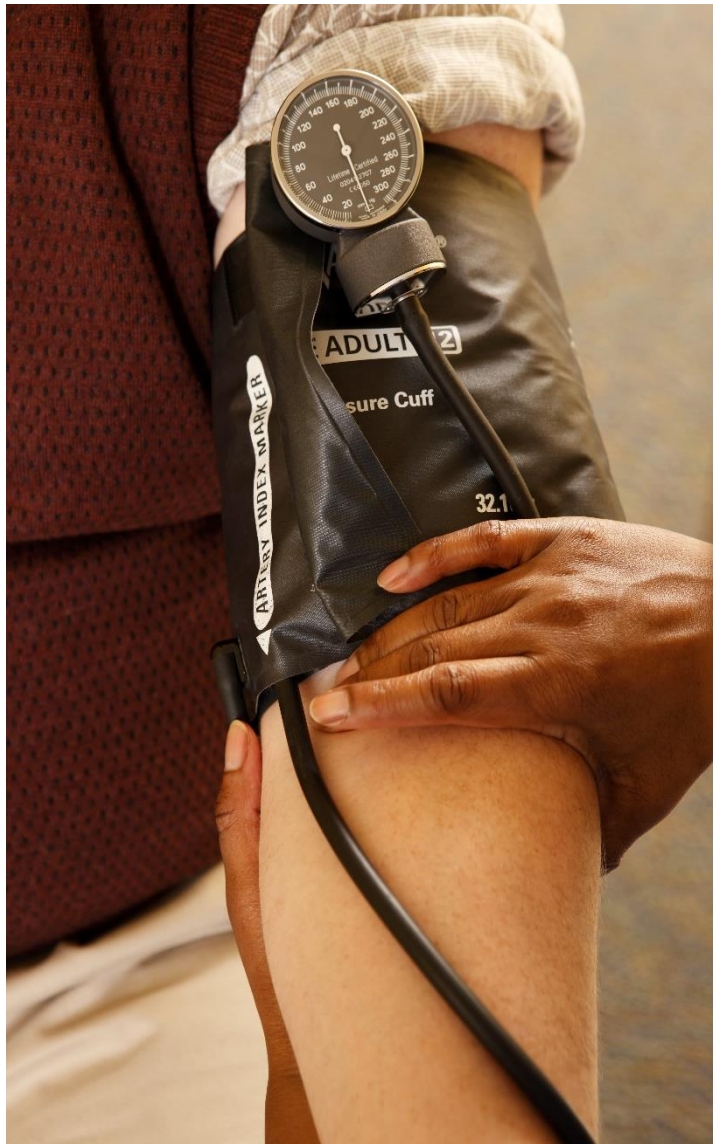
Conclusions

- Among patients with type 2 diabetes at high risk for cardiovascular events, a goal systolic BP <120 mm Hg was not superior to a goal <140 mm Hg

The ACCORD Study Group. N Engl J Med 2010;362:1575-85

ADA position statement on HTN and DM Standards of Care 2019

- For individuals with diabetes and hypertension at lower risk for cardiovascular disease (10-year ASCVD risk <15%), treat to a BP target of <140/90 mmHg. Level of evidence A.
- For individuals with diabetes and hypertension at higher cardiovascular risk (existing ASCVD or 10-year ASCVD risk >15%), a BP target of <130/80 mmHg may be appropriate, if it can be safely attained. Level of evidence C (supportive evidence from poorly controlled or uncontrolled studies).



9.3. Chronic Kidney Disease

Recommendations for Treatment of Hypertension in Patients With CKD References that support recommendations are summarized in Online Data Supplements 37 and 38 and Systematic Review Report.		
COR	**LOE**	**Recommendations**
I	SBP: B-R[SR] DBP: C-EO	1. Adults with hypertension and CKD should be treated to a BP goal of less than 130/80 mm Hg (1-6).
IIa	B-R	2. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void]), treatment with an ACE inhibitor is reasonable to slow kidney disease progression (3, 7-12).
IIb	C-EO	3. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio in the first morning void]) (7, 8), treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated.

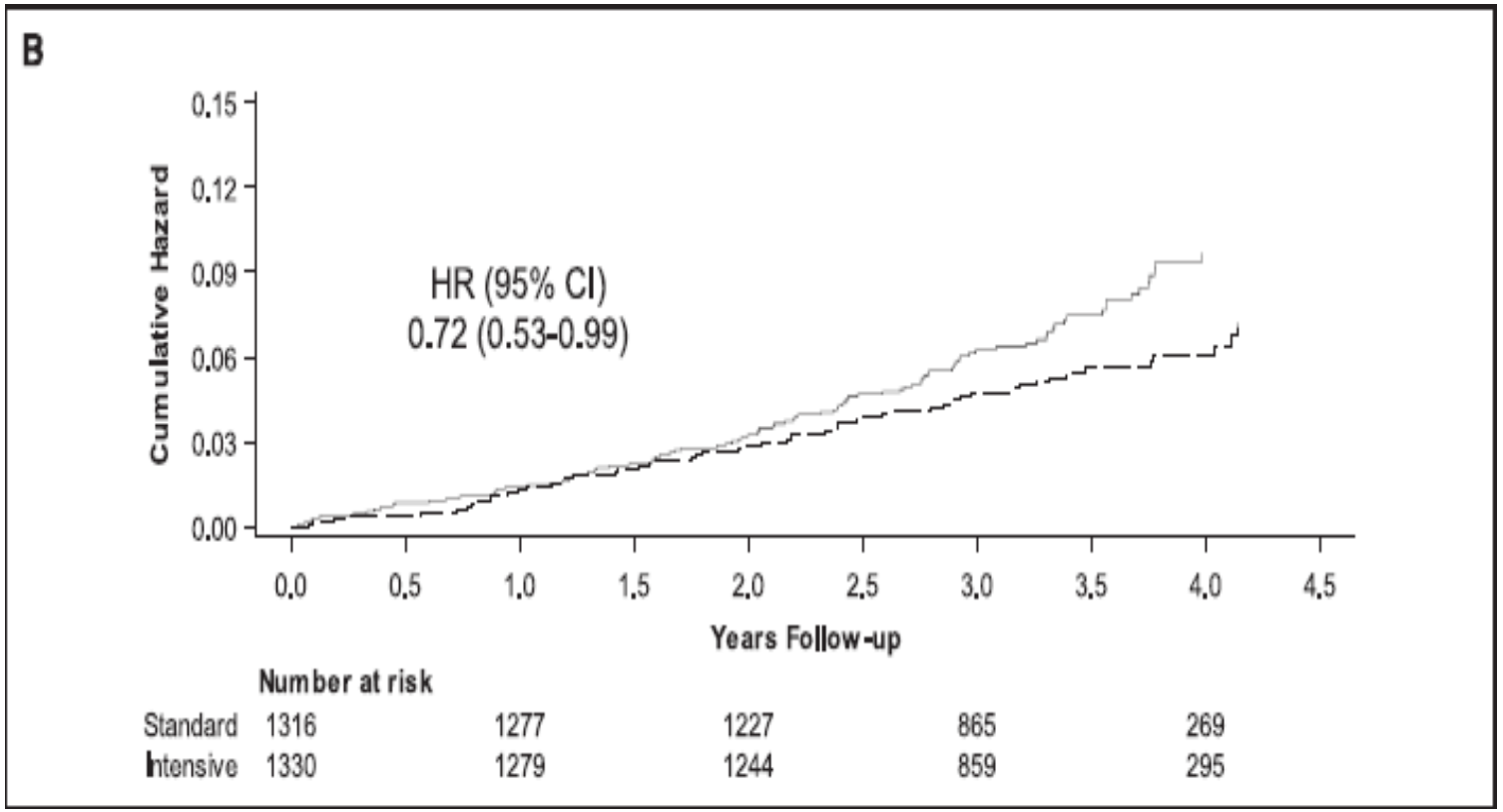
SR indicates systematic review.

SPRINT CKD

- Baseline Cr 1.43, GFR 48, ACR 81
- Medications used: 2.90 (intensive) vs. 2.02 (standard)
- Mean achieved BP – 135.3 (intensive) vs 123.0 (standard)
- Significant decrease in mortality – 28%
- No change in renal outcome (50% decline in GFR or ESRD)
- Change in GFR: -0.47 ml/min per year (intensive) vs. -0.32 ml/min per year (standard)
- Total SAEs same in both group, but more ARF, hypokalemia, hyperkalemia in intensive

J Am Soc Nephrol **28:** 2812–2823, 2017

All cause death



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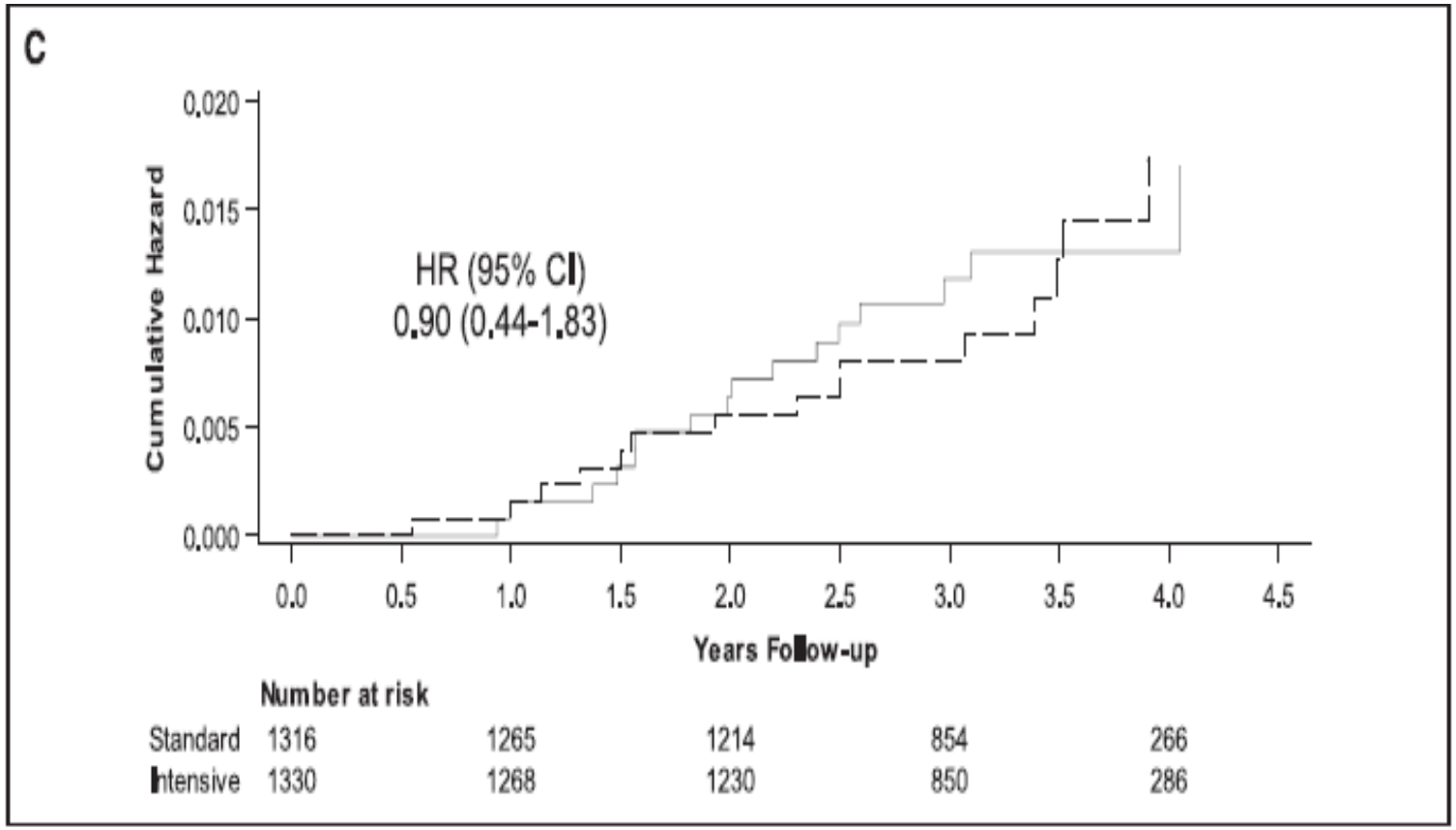
Renal outcome – 50% decline in GFR or ESRD



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NNT/NNH – SPRINT CKD

NNT at 4 years:

- primary composite outcome event - 66
- death from any cause - 28
- death from cardiovascular causes - 61

NNH:

- ARF – 35
- Hypokalemia – 131
- Hyperkalemia - 41

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Back to our Patient Case

80 year old woman with repeat BP 154/82 on amlodipine 5 mg daily. Home BPs run 140-150 SBP. She has normal cognition but considers herself somewhat frail (difficulty with some household duties, climbing a few flights of stairs). Community dweller; 10 year CVD risk of 24%.

Her goal BP is < 130/90.

Intensive treatment would be expected to decrease CV outcomes and MCI, but possibly increase adverse events (SPRINT general: hypotension, electrolyte abnormalities, ARF; SPRINT 75: hyponatremia).

Conclusions

- Goal < 140/90 for all
- SBP goal < 130 for SPRINT high risk: 75+, CVD, CKD (GFR 20-59), 10 year CVD risk ≥ 15%
- Consider same goal for frail elderly
- Intensive treatment: improved CV outcomes, MCI, possible dementia, but with some increase in adverse events.
- BP measurement is important!