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Ohio Cardiovascular Health Collaborative

SCHOOL OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY

In partnership with

THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER

COLLEGE OF MEDICINE AND LIFE SCIENCES THE UNIVERSITY OF TOLEDO

OHIO UNIVERSITY Heritage College of Osteopathic Medicine

Northeast Ohio MEDICAL UNIVERSITY

University of CINCINNATI FAMILY AND COMMUNITY MEDICINE

Boonshoft School of Medicine WRIGHT STATE UNIVERSITY

MedTAPP

OHIO COLLEGES OF MEDICINE GOVERNMENT RESOURCE CENTER

Ohio Department of Medicaid

March 2019

Safety and Tolerability of Lower Blood Pressure Targets

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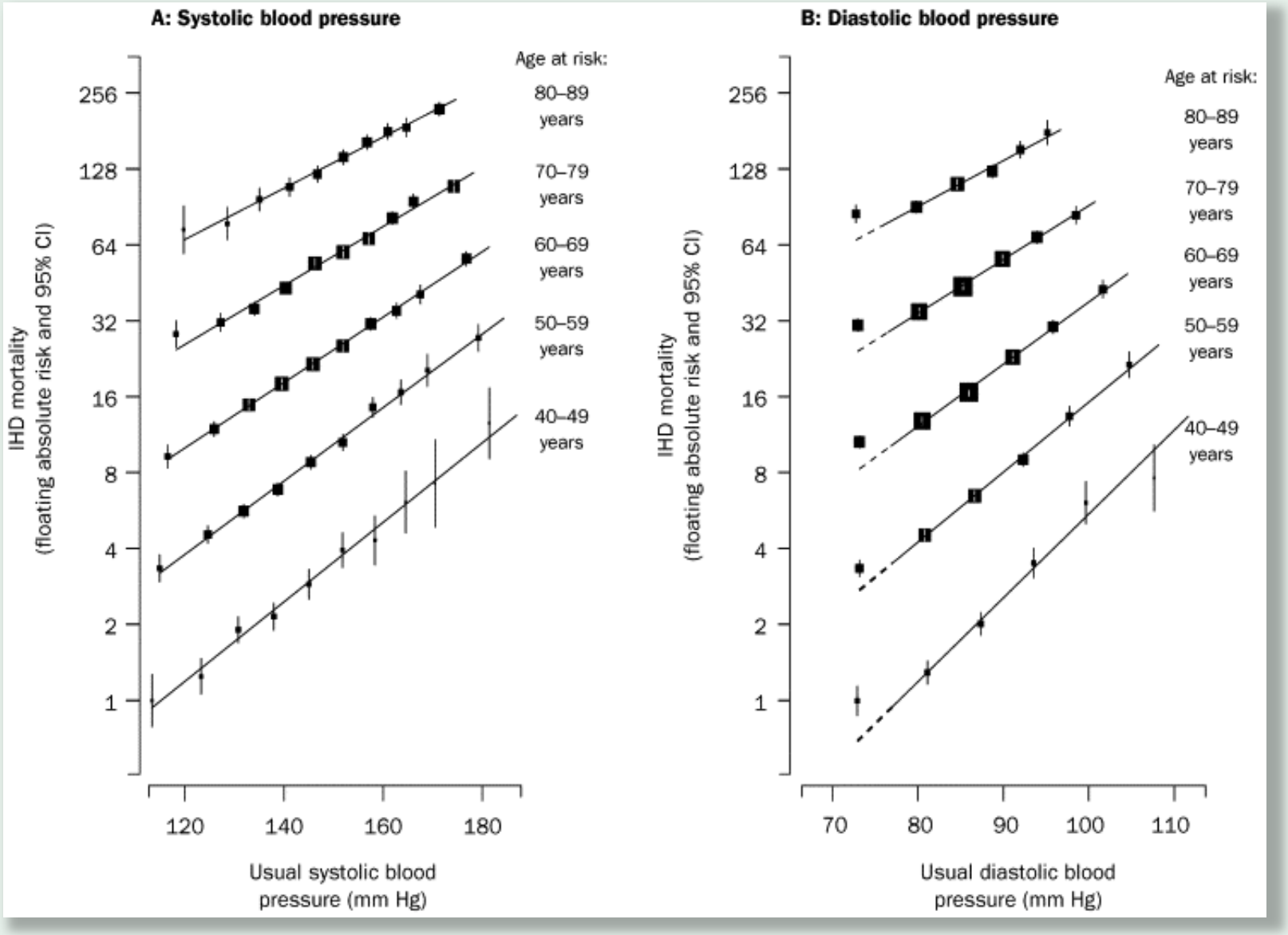
Topics Covered

- Relationship of cardiovascular risk with blood pressure in epidemiologic and blood pressure treatment trials
- SPRINT Trial results showing reduction in clinical outcomes in diverse patient population by race, ethnicity, and age (above and below age 75 yrs)
- Blood pressure control achieved in SPRINT using one of the Cardi-OH algorithms
- Tolerability of SPRINT intensive blood pressure target

Hypertension and IHD Mortality

The higher the BP (SBP or DBP) the greater the risk of death from CVD

- Observational (epidemiologic) studies show that the higher the BP (SBP or DBP), the greater the risk of death from cardiovascular disease
- The older the patient, the greater the risk



Prospective Studies Collaboration. Lancet 2002; 360:1903-13

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Hazard Ratios (95% CI) for Major Cardiovascular Disease at Different Levels of Achieved Systolic BP

- Meta-analyses of hypertension treatment trials showing the lower the SBP achieved in the trials, the lower the risk for stroke, CHD, and death from any cause
- Progressive reduction in risk of CVD at lower levels of achieved SBP down to levels below current European & US recommendations
- Similar findings for stroke, CHD and all-cause mortality
- Similar pattern in a sensitivity analyses where:
  - SPRINT results excluded
  - Results from four trials with risk or lack of clarity for bias
- No inconsistency between direct or network (indirect) comparisons
- No inconsistency for CVD benefit in several other meta-analyses (including Xie et al., Verdecchia et al., and Bangalore et al.)

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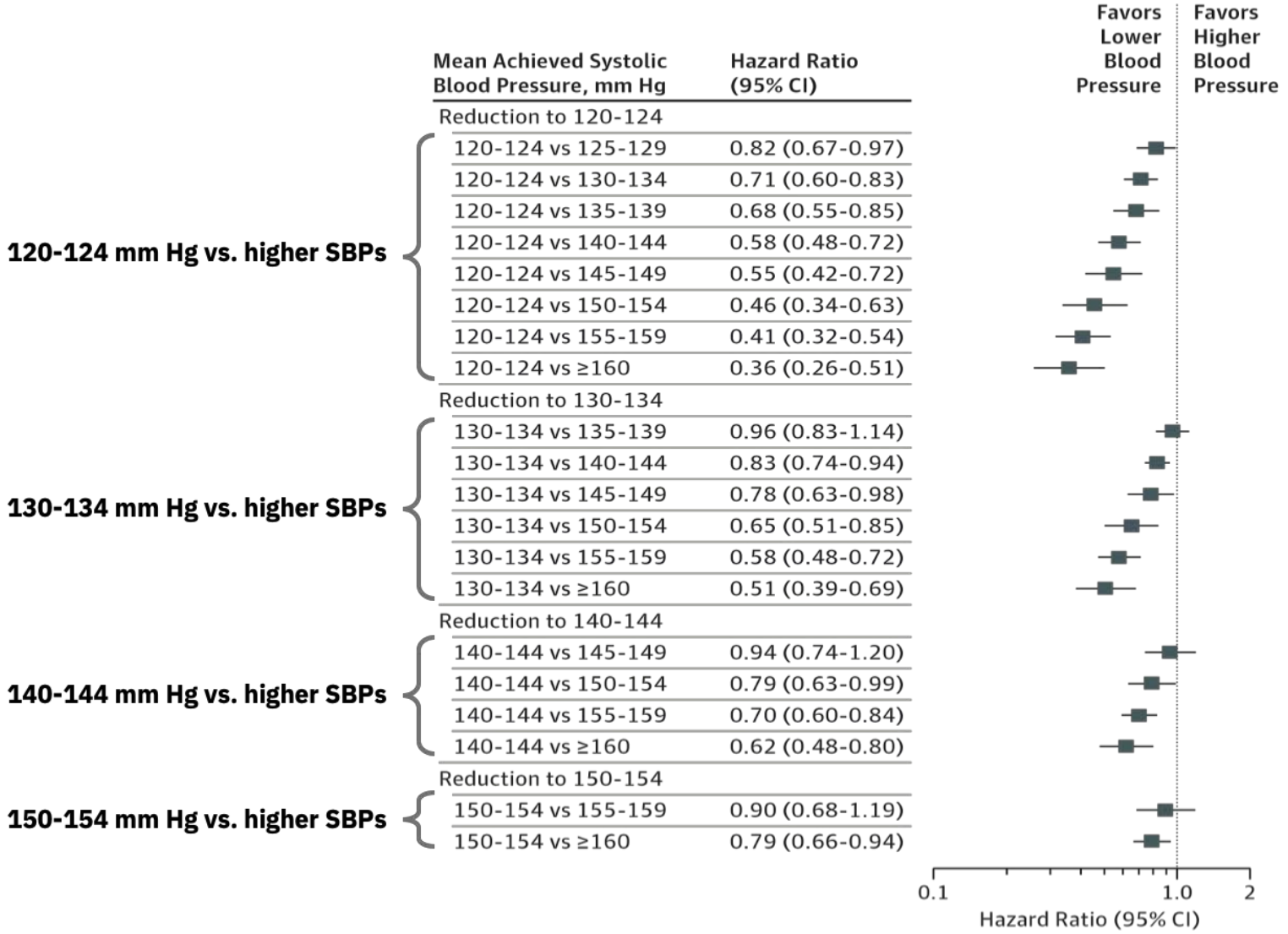
Network Meta-analysis (42 RCTs: N = 144,220)



Bundy JD et al. JAMA Cardiol 2017; 2:775-781

Systolic BP Intervention Trial (SPRINT)

- SPRINT compared the effect of treating to a SBP target of < 120 mmHg vs treatment to < 140 mmHg
- Sprint Trial recruited a diverse population of 9,361 patients with elevated CVD risk:
  - 28% over age 75
  - ~30% African American
  - ~11% Hispanic

Demographic and Baseline Characteristics			
Trial	*Total N=9361*	*Intensive N=4678*	*Standard N=4683*
Mean (SD) age, years	67.9 (9.4)	67.9 (9.4)	67.9 (9.5)
% ≥75 years	28.2%	28.2%	28.2%
Female, %	35.6%	36.0%	35.2%
White, %	57.7%	57.7%	57.7%
African-American, %	29.9%	29.5%	30.4%
Hispanic, %	10.5%	10.8%	10.3%
Prior CVD, %	20.1%	20.1%	20.0%
Mean 10-year Framingham CVD risk, %	24.8%	24.8%	24.8%
Taking antihypertensive meds, %	90.6%	90.8%	90.4%
Mean (SD) number of antihypertensive meds	1.8 (1.0)	1.8 (1.0)	1.8 (1.0)
Mean (SD) Baseline BP, mm Hg			
Systolic	139.7 (15.6)	139.7 (15.8)	139.7 (15.4)
Diastolic	78.1 (11.9)	78.2 (11.9)	78.0 (12.0)

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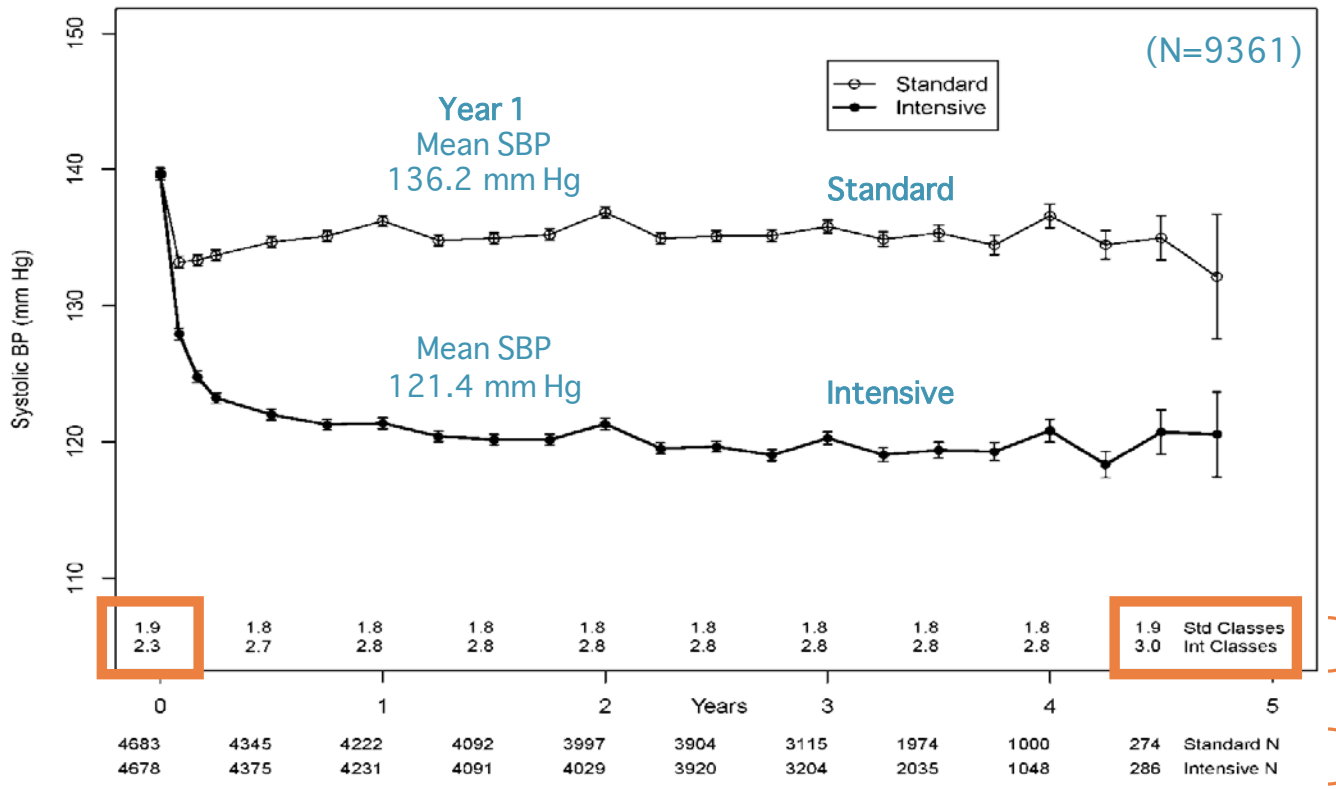
SPRINT Trial

- Good BP separation achieved, with those randomized to < 120 mmHg requiring on average one more BP medication than those randomized to the <140 mmHg target
- BP separation continued throughout trial follow-up

Mean Systolic BP (95% CI)



Average SBP
During Follow-up

Standard
134.6 mm Hg

Intensive
121.5 mm Hg

Average number of anHypertensive medications

Number of participants

SPRINT Research Group. NEJM 2015; 373:2103-2116

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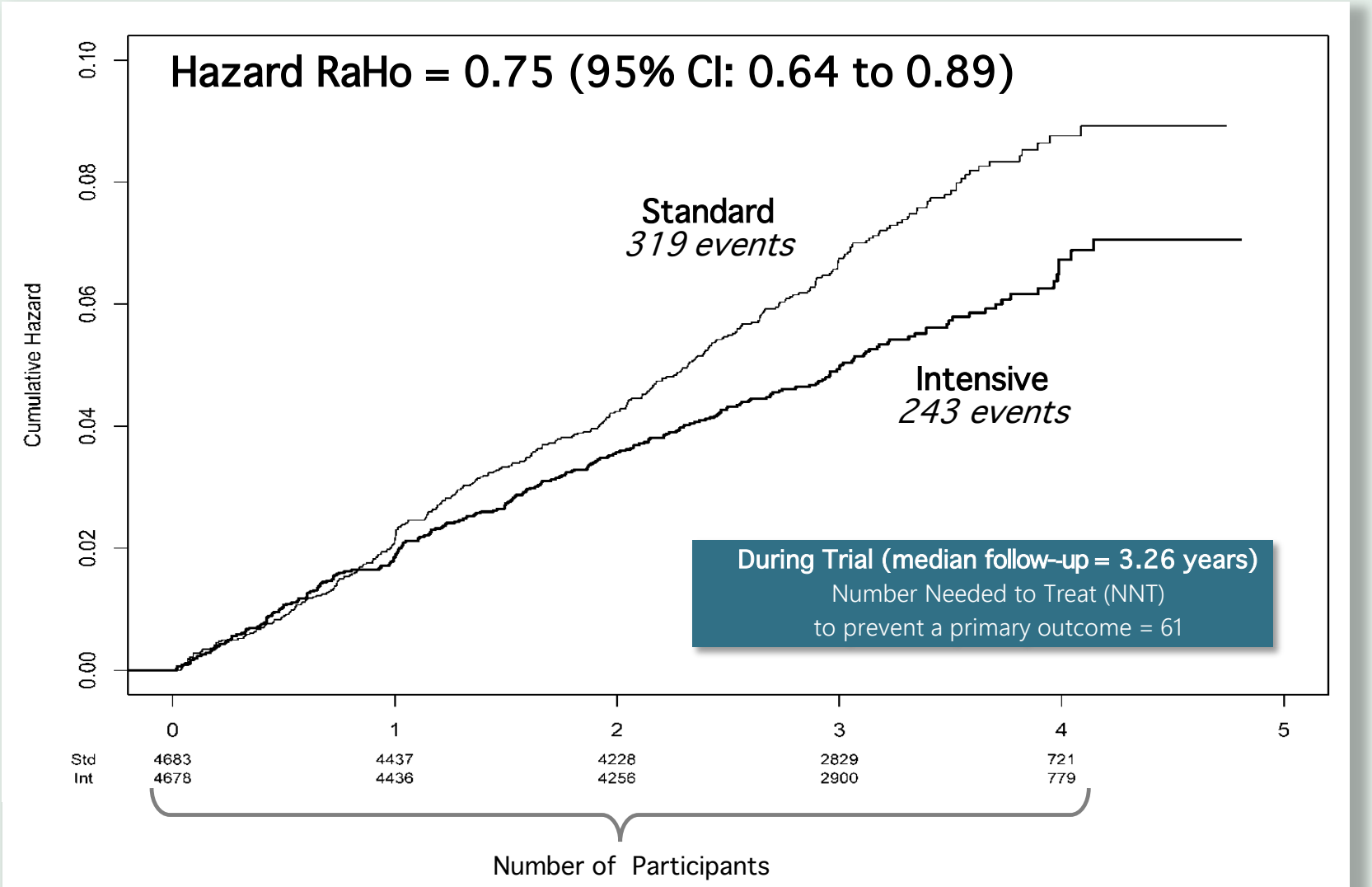
SPRINT Primary Outcome* Cumulative Hazard

- *Results:*
  - Separation beginning at ~ 1 yr of f/u
  - 25% reduction in primary outcome (mostly heart failure, stroke, heart attacks, and cardiovascular death)*
  - 27% reduction in death from any cause
- Trial stopped early at the recommendation of the data safety and monitoring board unless those in the <140 cohort informed of the dramatic benefit of the < 120 mmHg target

  * MI, ACS other than MI, Stroke, Heart Failure**, Death from CV Causes**

  ** Primary Endpoints and Mortality Significantly Reduced



SPRINT Research Group. NEJM 2015; 373:2103-2116

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SPRINT Primary Outcome and Its Components

- All-cause mortality was reduced by 27%
- These are hard and non-reversible outcomes which, unlike most of the AEs and SAEs reported, carry substantial long term consequences
- NNT for 1° outcome = 61 and 90 for all-cause mortality

Event Rates and Hazard Ratios

	Intensive		Standard			
	# of Events	Rate, %/yr	# of Events	Rate, %/yr	HR (95% CI)	P-Value
Primary Outcome	243	1.65	319	2.19	0.75 (0.64, 0.89)	<0.001
All MI	97	0.65	116	0.78	0.83 (0.64, 1.09)	0.19
Non-MI ACS	40	0.27	40	0.27	1.00 (0.64, 1.55)	0.99
All Stroke	62	0.41	70	0.47	0.89 (0.63, 1.25)	0.50
All HF	62	0.41	100	0.67	0.62 (0.45, 0.84)	0.002
CVD Death	37	0.25	65	0.43	0.57 (0.38, 0.85)	0.005
Total Mortality	155	1.03	210	1.40	0.73 (0.60, 0.90)	0.003

SPRINT Research Group. NEJM 2015; 373:2103-2116

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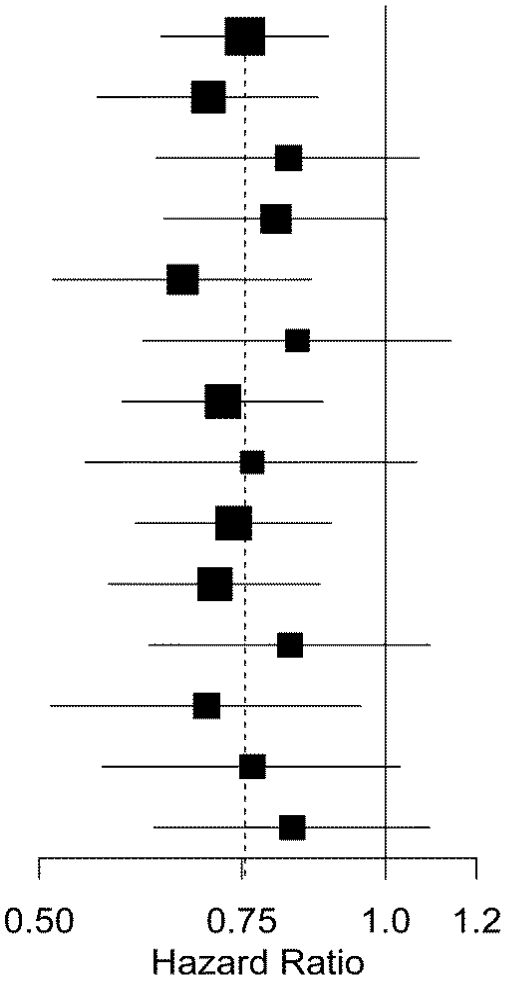
SPRINT Primary Outcome Experience in the 6 Pre-Specified Subgroups of Interest

- Benefit seen in all pre-specified subgroups
- Benefit also seen in Hispanic patients

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.

SPRINT Research Group. NEJM 2015; 373:2103-2116

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Key SPRINT Trial Findings by Race and Ethnicity

- The primary outcome was similarly reduced in all subgroups as well as CV death and the composite of the primary outcome and all cause mortality. P-value interaction not significant indicating no difference by race/ethnic subgroup
- There was a significant interaction for all-cause mortality and a suggestion that Hispanics had higher all-cause mortality in the Intensive arm
- However cardiovascular mortality was if anything reduced more in Hispanics randomized to the Intensive arm though the numbers were small
- Non CV mortality that was increased in the Intensive arm in Hispanics, though again the numbers were small
- Guidance – revision of data as presented in journal article. Use as is
- NWH=Non-Hispanic Whites; NHB=Non-Hispanic Blacks

Primary and Secondary Outcomes Stratified by Treatment Group and Race-Ethnicity.

		Intensive Arm		Standard Arm		Intensive vs. Standard Hazard Ratio			
		Events	%/Yr	Events	%/Yr	HR	Lower 95% CL	Upper 95% CL	Interaction P-Value
Primary Outcome	NHW	167	1.9	229		2.7	0.70	0.57	
	NHB	64	1.5	93		2.1	0.71	0.51	0.85
	Hispanic	20	1.2	26		1.7	0.62	0.33	
Cardiovascular Health	NHW	23	0.3	45		0.5	0.49	0.29	
	NHB	13	0.3	18		0.4	0.77	0.37	0.098
	Hispanic	1	0.1	6		0.4	0.17	0.01	
Primary Outcome or Death	NHW	222	2.6	310		3.6	0.70	0.59	
	NHB	94	2.2	122		2.7	0.78	0.59	0.082
	Hispanic	35	2.1	31		2.0	1.00	0.60	

Adapted from Still CH et al. Am J Hypertens 2017 Dec 8;31(1):97-107.

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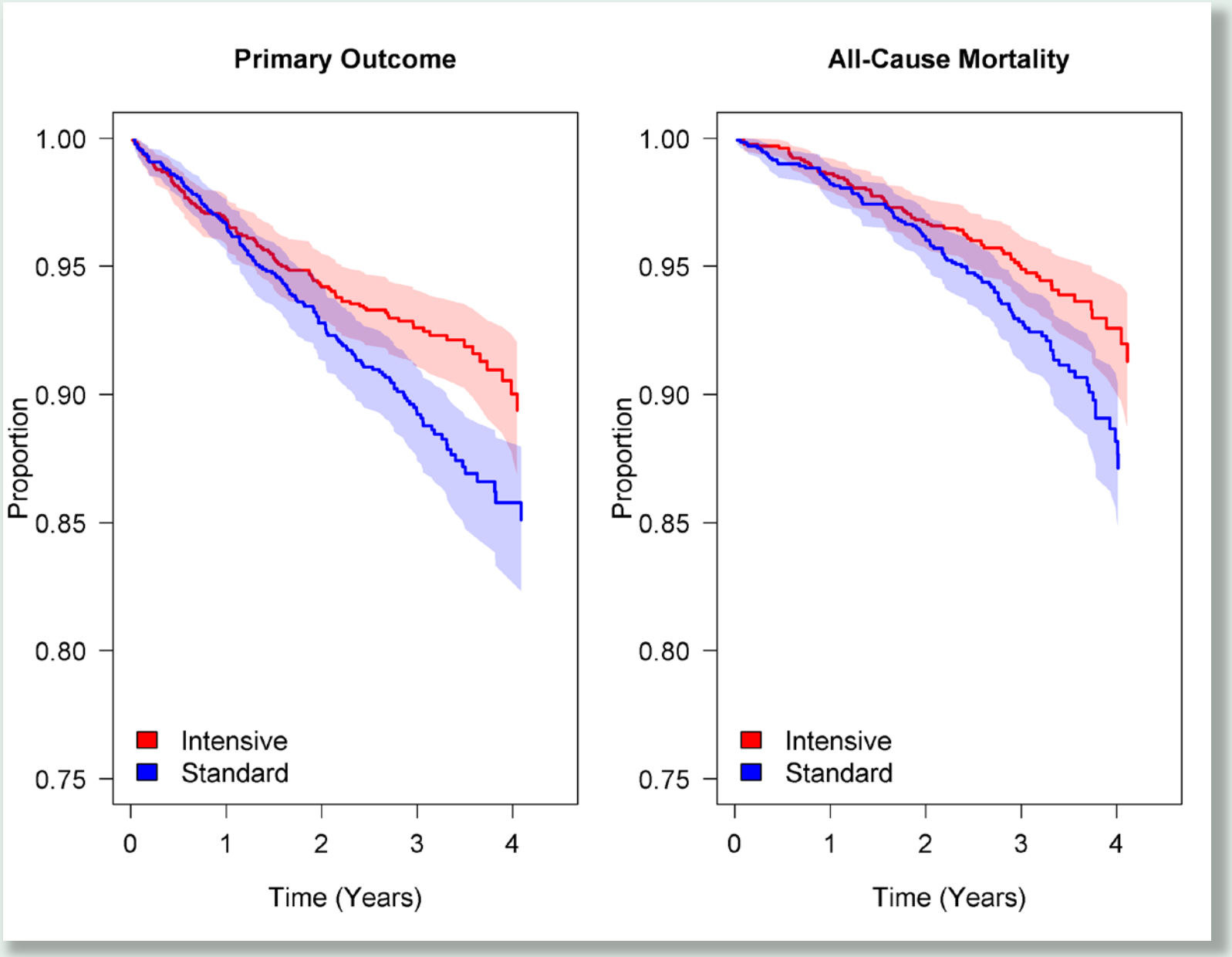
SPRINT Kaplan-Meier Survival Curves for Primary Outcome and All-Cause Mortality in Participants 75 and Older

- Mean and median age in SPRINT was 68 years-old
- 28% of participants were > age 75
- The number needed to treat to prevent a primary outcome was somewhat lower in those over age 75 yrs (28 vs. 61) and (41 vs. 90) for all-cause mortality



Willamson JD et al for the SPRINT Research Group; JAMA 2016; 315:2673-82

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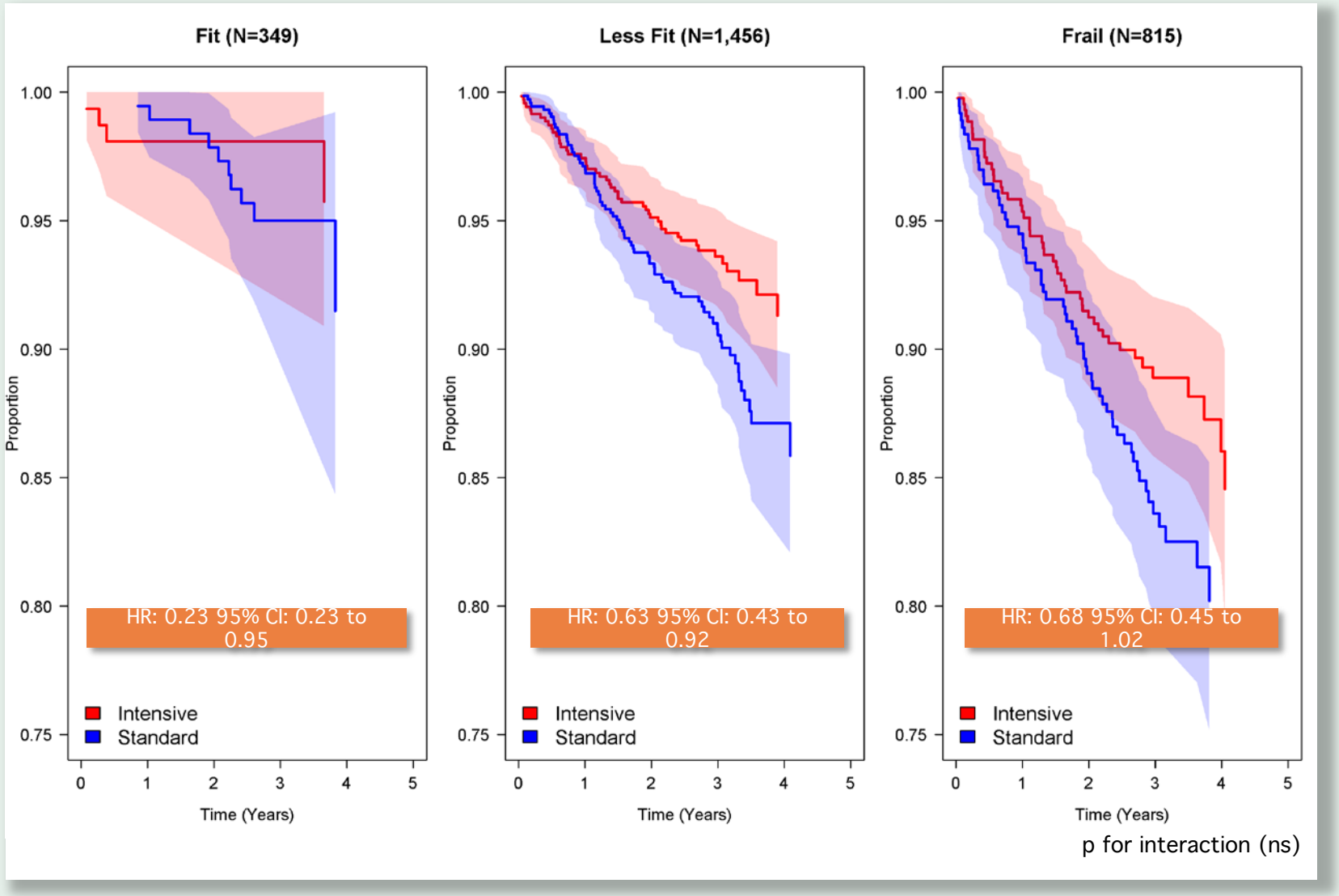
SPRINT Kaplan-Meier Survival Curves for Primary Outcome by Frailty Status

- Survey questionnaire and timed 4-meter walk used to assess frailty in those over age 75
- No significant difference and benefit of < 120 mmHg target seen in fit, less fit, and frail
- Nursing home residents, those with < 3 yr expected survival, and those with dementia at baseline were excluded



Willamson JD et al for the SPRINT Research Group; JAMA 2016; 315:2673-82

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SPRINT Serious Adverse Events (SAE) During Follow-up

- SAE = fatal or life threatening event, resulting in significant or persistent disability, requiring or prolonging hospitalization, or judged an important medical event
- Large number of overall serious adverse events (SAE) in both treatment groups in this high risk population
- However, no significant difference in SAEs by treatment group, even in those over age 75 years of age

	Number (%) of Participants		
	Intensive	Standard	HR (P Value)
All SAE reports (Overall cohort)	1793 (38.3)	1736 (37.1)	1.04 (0.25)
All SAE reports (age > 75 years)	640 (48.6)	638 (48.4)	1.00 (0.93)

SPRINT Research Group

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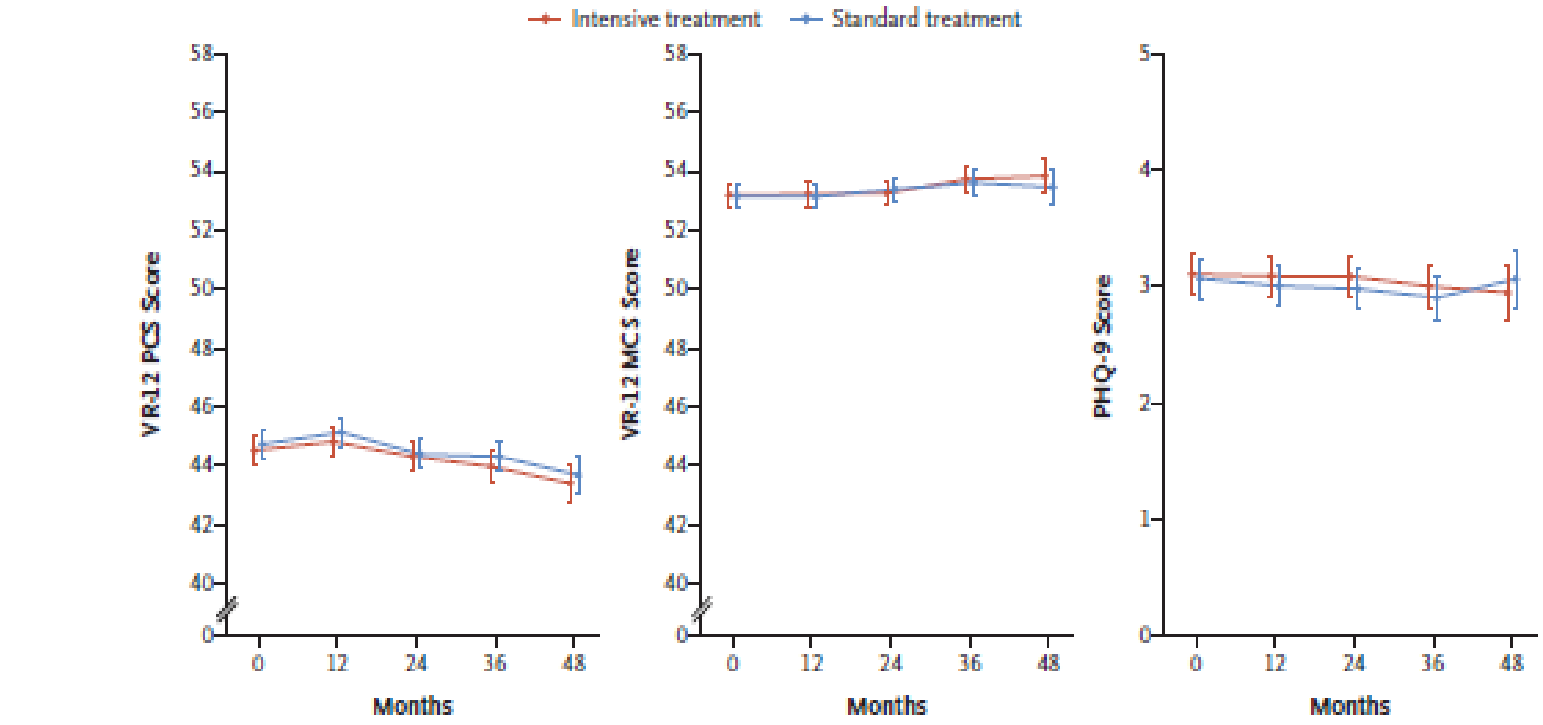
SPRINT Tolerability of the < 120 mmHg SBP Target

- Health-related quality of life measured using physical and mental components of VR-12 and depressive sxs using PHQ-9 shows no difference in patient-reported quality of life overall, including no significant difference in those over age 75

Patient-Reported Outcomes in the Two Treatment Groups, Over Time



No. of Participants					
Intensive treatment	4657	4276	4112	2919	805
Standard treatment	4662	4266	4083	2877	774
Intensive treatment	4654	4269	4109	2919	804
Standard treatment	4659	4262	4078	2876	774
Intensive treatment	4655	4267	4105	2919	805
Standard treatment	4659	4261	4078	2874	774

Berlowitz DR et al. NEJM 2017; 377:733-44.

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