Systolic Blood Pressure Intervention Trial (SPRINT)

Principal Results

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For the SPRINT Research Group

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Background

- *Observational studies identify strong association between BP and risk of CVD, with no evidence of threshold for the relationship*
- *High BP very common*
  - *High SBP leading risk factor for mortality and disability-adjusted life years*
  - *Worldwide, >1 billion adults have hypertension*
- *Clinical trials demonstrate antihypertensive drug therapy reduces risk of CVD*
- *However, optimal target for SBP lowering uncertain*

SPRINT Research Question

Examine effect of more intensive high blood pressure treatment than is currently recommended

Randomized Controlled Trial
Target Systolic BP

Intensive Treatment
Goal SBP < 120 mm Hg

Standard Treatment
Goal SBP < 140 mm Hg

SPRINT design details available at:

- *ClinicalTrials.gov (NCT01206062)*
- *Ambrosius WT et al. Clin. Trials. 2014;11:532-546.*

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

At least one

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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*

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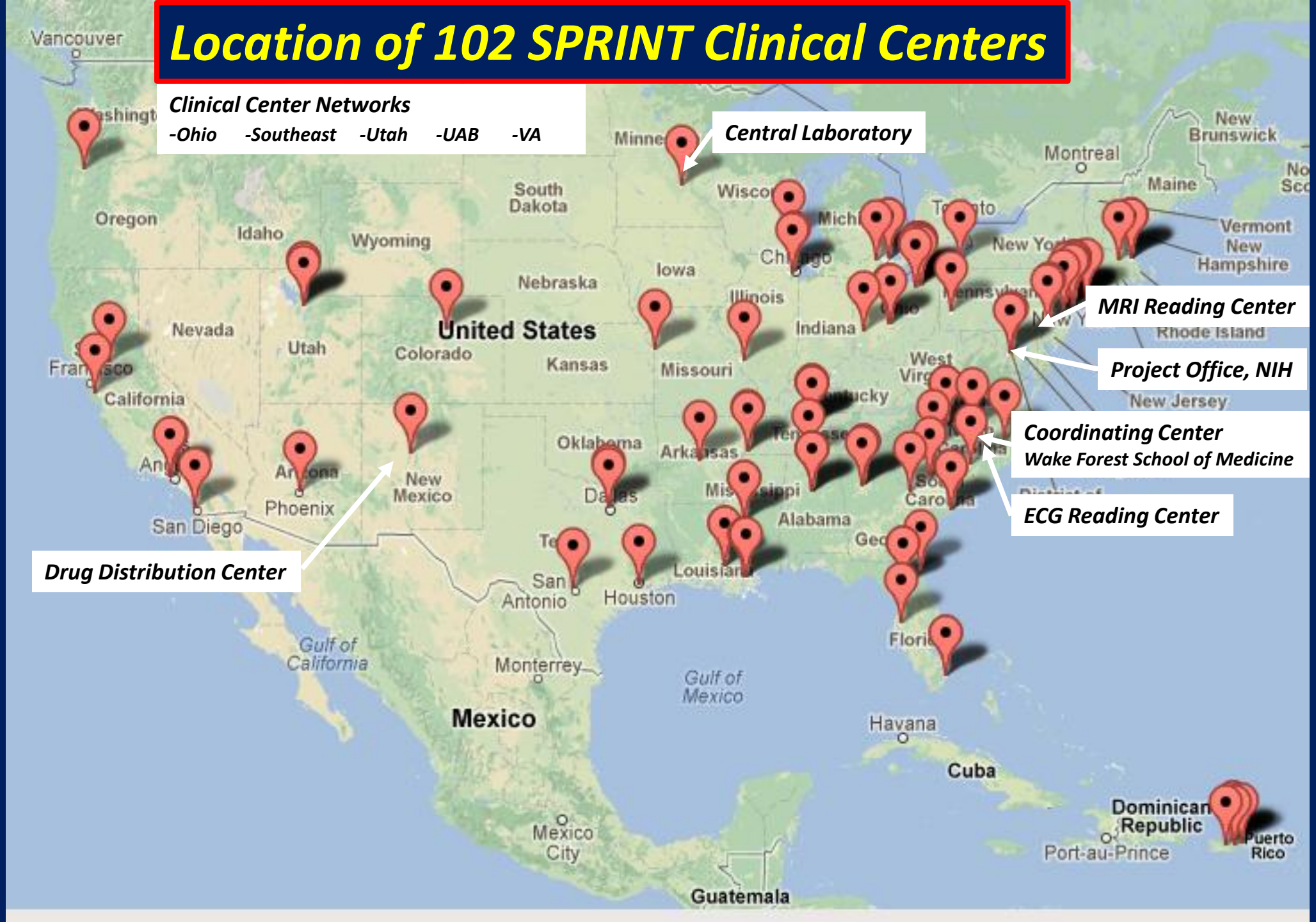
Location of 102 SPRINT Clinical Centers



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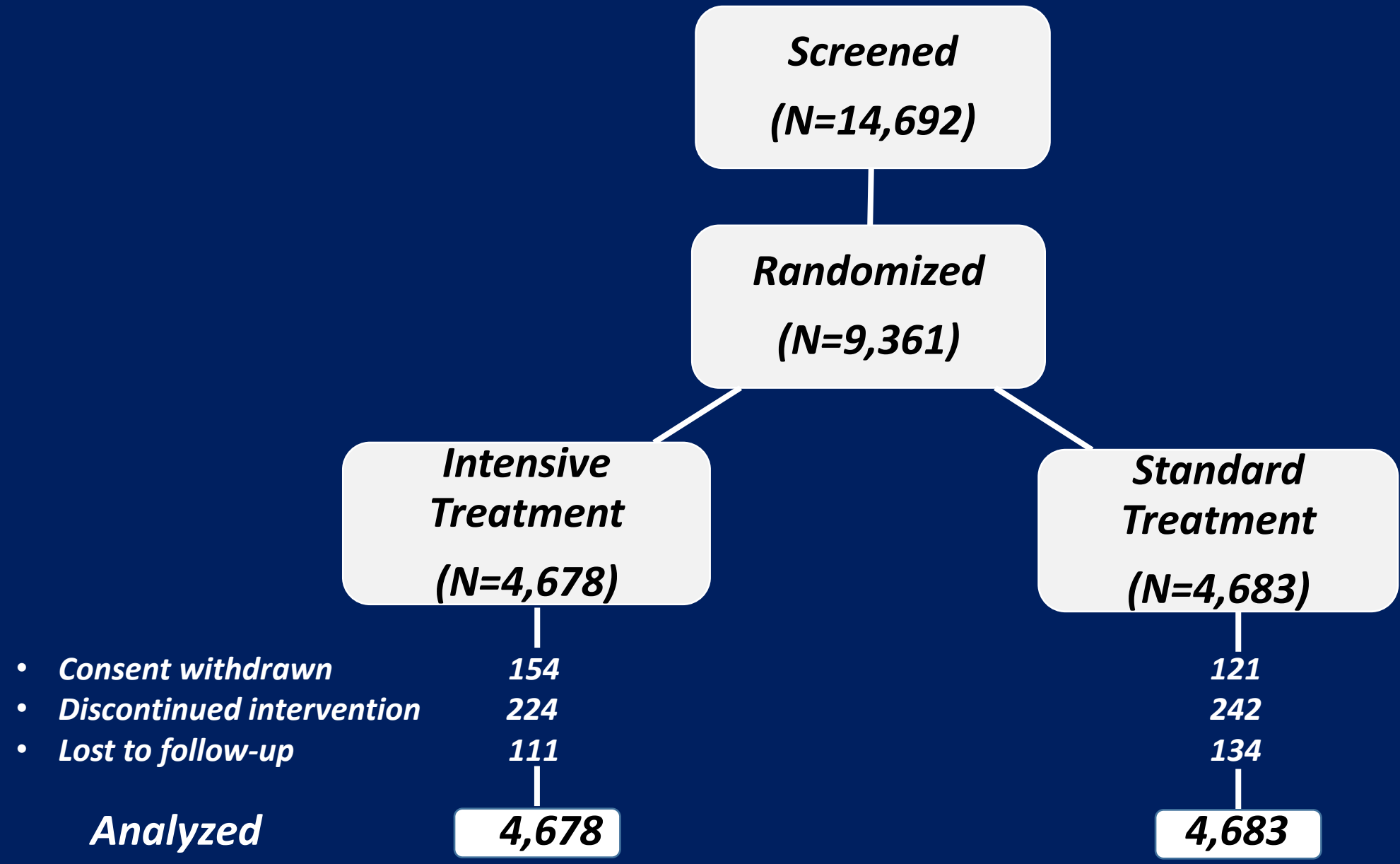
SPRINT: Enrollment and Follow-up Experience



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Demographic and Baseline Characteristics

	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, %	20.1%	20.1%	20.1%
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)

Selected Baseline Laboratory Characteristics

	Total N=9361	Intensive N=4678	Standard N=4683
Mean (SD) eGFR, mL/min/1.73 m^2	71.7 (20.6)	71.8 (20.7)	71.7 (20.5)
% with eGFR<60 mL/min/1.73m^2	28.3	28.4	28.1
Mean (SD) Urine albumin/creatinine, mg/g	42.6 (166.3)	44.1 (178.7)	41.1 (152.9)
Mean (SD) Total cholesterol, mg/dL	190.1 (41.2)	190.2 (41.4)	190.0 (40.9)
Mean (SD) Fasting plasma glucose, mg/dL	98.8 (13.5)	98.8 (13.7)	98.8 (13.4)

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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)*

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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.

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Additional Outcomes

- *All-cause mortality*
- *Primary outcome + all-cause mortality*
- *Renal*
  - *Main secondary outcome:*
    - *Participants with CKD at baseline: incidence of decline in eGFR ≥50% or ESRD*
  - *Additional secondary outcomes:*
    - *Participants without CKD at baseline: incidence of decline in eGFR ≥30%* (to <60 mL/min/1.73m^2)
    - *Participants with or without CKD at baseline: Incidence of albuminuria* — *Doubling of urinary albumin/creatinine (<10 to >10 mg/g)*

Follow-up Assessment of Selected Measures

- CVD outcomes
  - Pre-specified diagnostic criteria
  - Ascertainment method identical in both treatment arms
    - Structured interview every 3 months
  - Possible events adjudicated by a panel of experts, blinded to treatment assignment
- Fatal events
  - Structured approach to collection of information
  - Cause of death adjudicated by the panel of experts, blinded to treatment assignment
- Safety events
  - Could be reported at any SPRINT visit
  - Observers aware of treatment assignment
- Labs: blood chemistries and urine albumin/creatinine

BP Intervention

- *BP monitored monthly for 3 months and every 3 months thereafter (additional visits could be scheduled)*
- *Antihypertensive medication titration decisions based on mean BP (3 readings at each visit), using a structured stepped-care approach*
- *Agents from all major antihypertensive drug classes available free of charge*
- *Periodic assessment for orthostatic hypotension and related symptoms*

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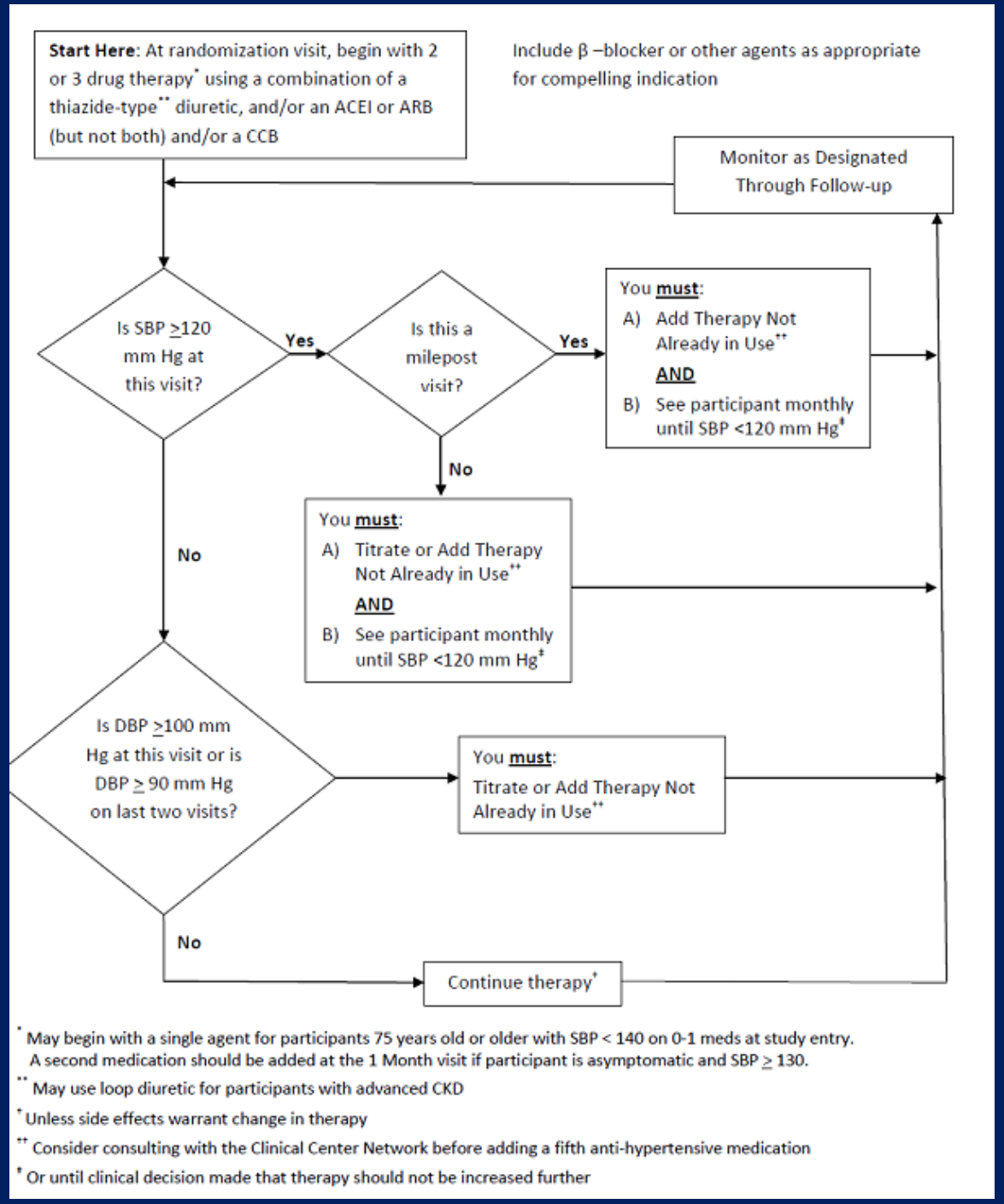
SPRINT Treatment Algorithm

Intensive Treatment



* May begin with a single agent for participants 75 years old or older with SBP < 140 on 0-1 meds at study entry. A second medication should be added at the 1 Month visit if participant is asymptomatic and SBP ≥ 130.

** May use loop diuretic for participants with advanced CKD

† Unless side effects warrant change in therapy

†† Consider consulting with the Clinical Center Network before adding a fifth anti-hypertensive medication

‡ Or until clinical decision made that therapy should not be increased further

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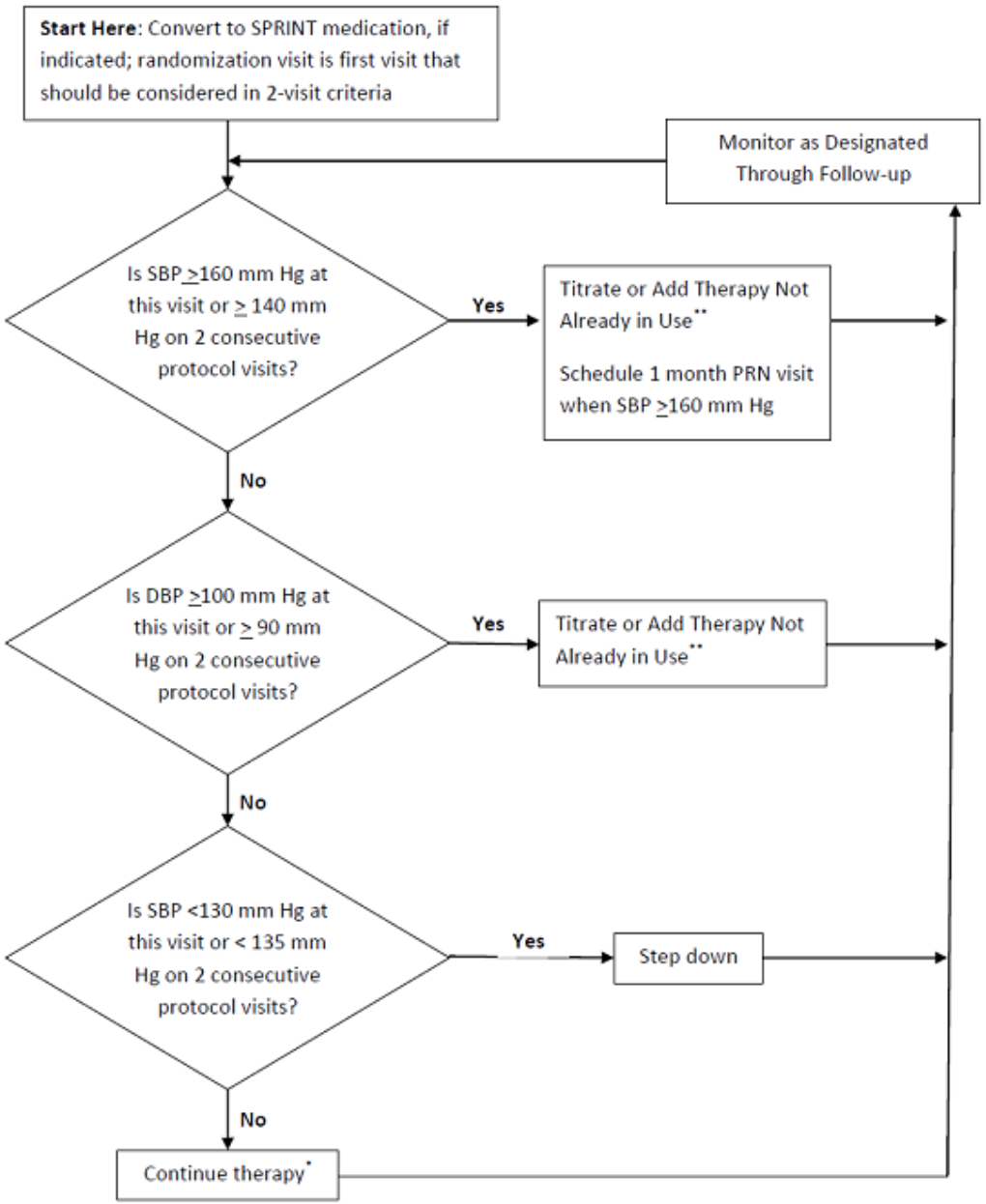
SPRINT Treatment Algorithm

Standard Treatment



Include β –blocker or other agents as appropriate for compelling indications

* Unless side effects warrant change in therapy

** Consider consulting with the Clinical Center Network before adding a fifth anti-hypertensive medication

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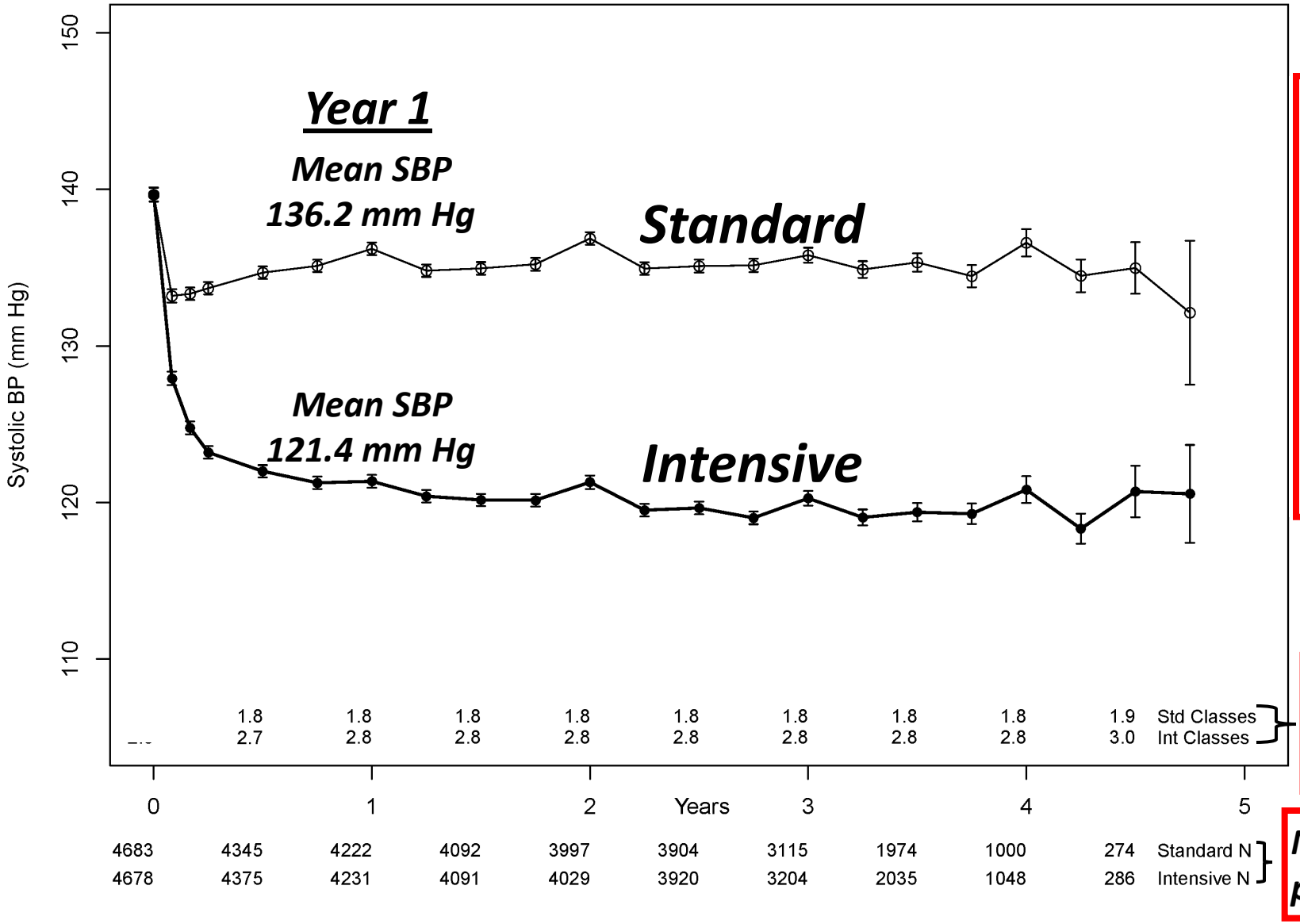
Systolic BP During Follow-up



Average SBP
(During Follow-up)

Standard: 134.6 mm Hg

Intensive: 121.5 mm Hg

Average number of antihypertensive medications

Number of participants

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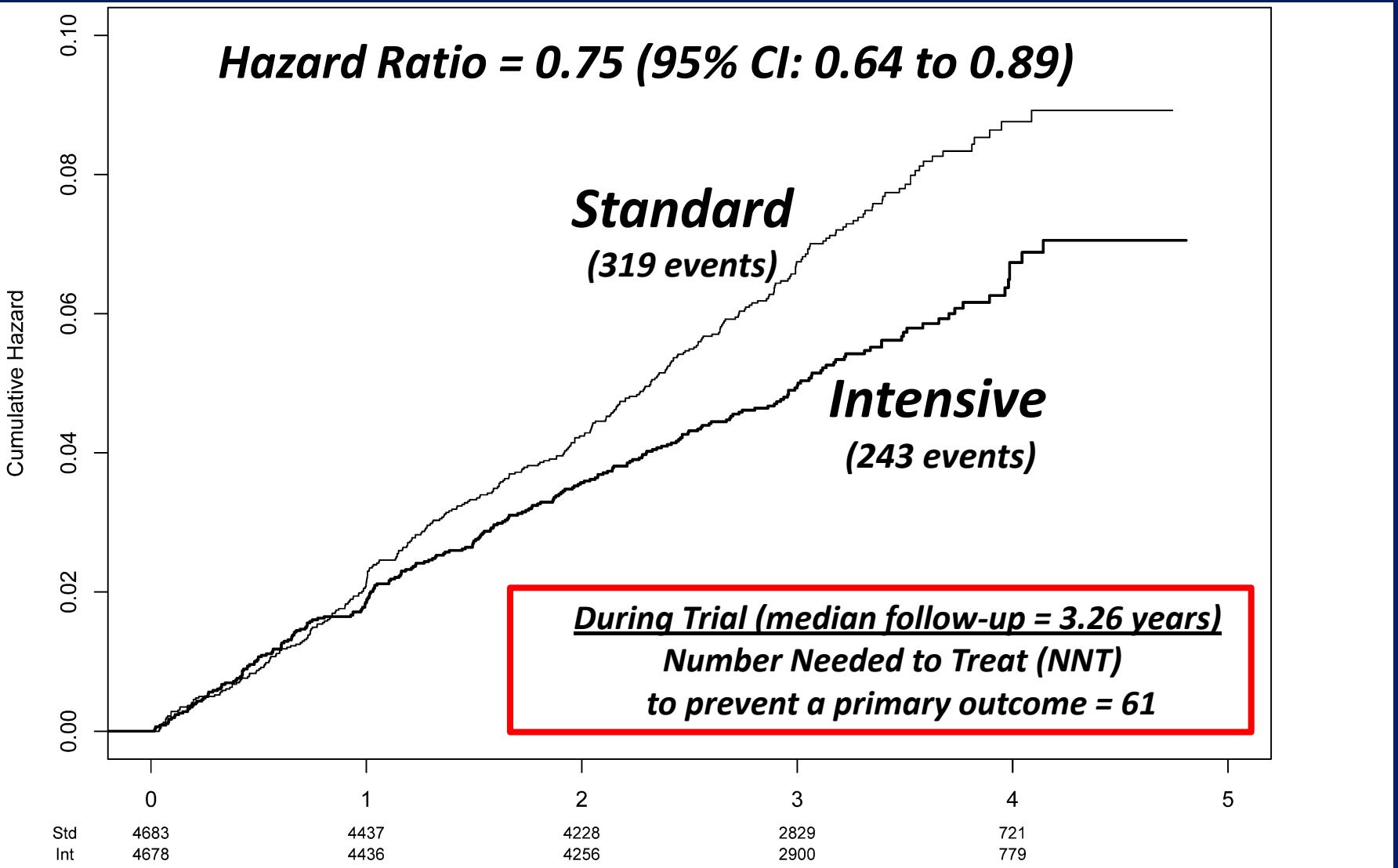
Decision to Stop BP Intervention

- *On August 20th, 2015, NHLBI Director accepted DSMB recommendation to inform SPRINT investigators and participants of CVD results*
- *Concurrently, decision made to stop BP intervention*
- *This presentation based on adjudicated events that occurred through August 20th, 2015*
  - *Median follow-up = 3.26 years*
- *Data for some secondary non-CVD outcomes (e.g. dementia and cognitive impairment) being collected at final close-out visit and this process will be completed in 2016*

SPRINT Primary Outcome
Cumulative Hazard



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SPRINT Primary Outcome and its Components

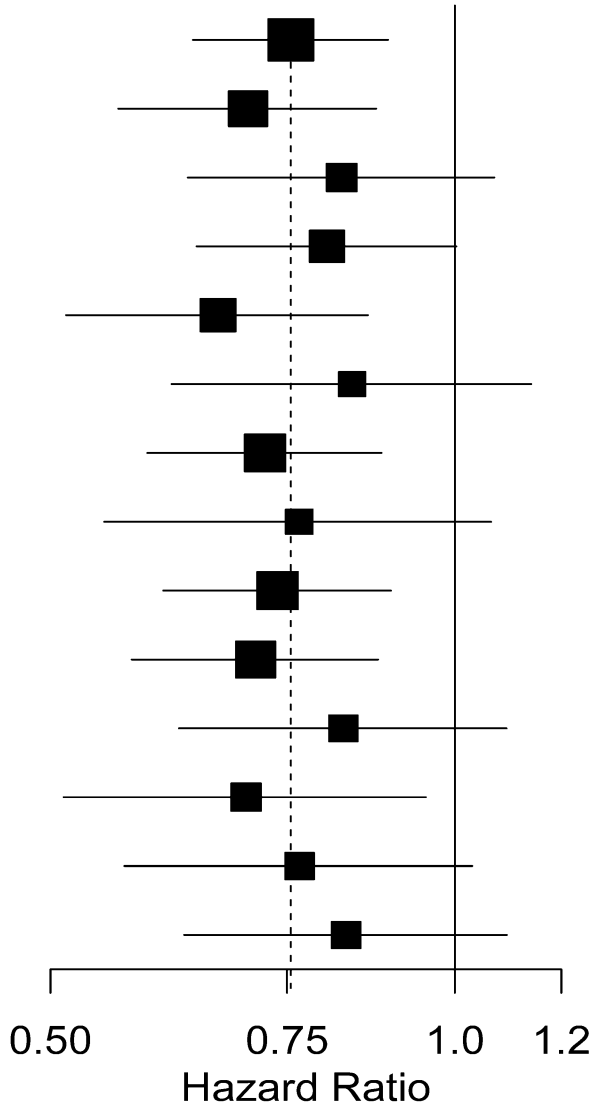
Event Rates and Hazard Ratios

	Intensive		Standard			
	No. of Events	Rate, %/year	No. of Events	Rate, %/year	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

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



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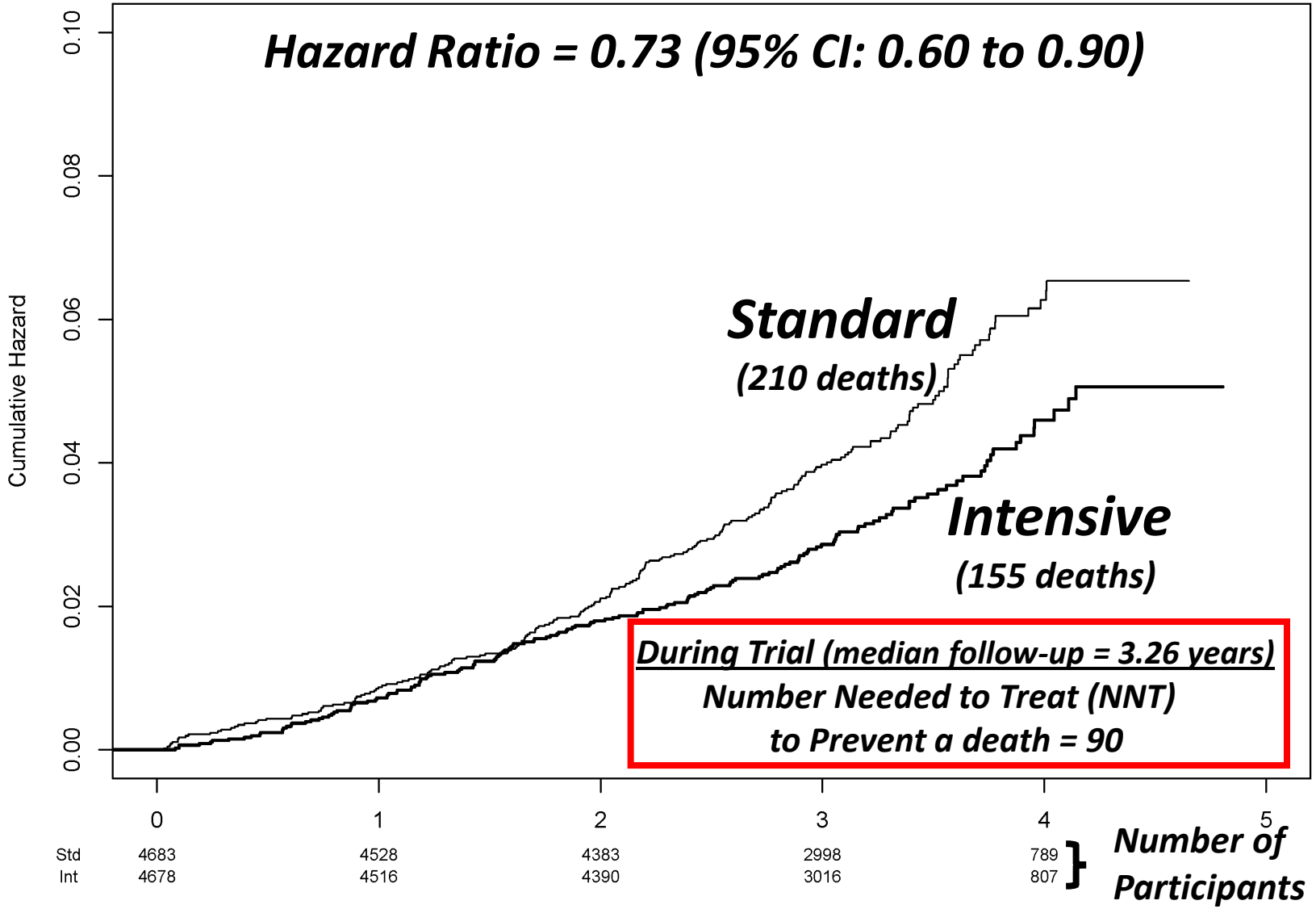
All-cause Mortality
Cumulative Hazard



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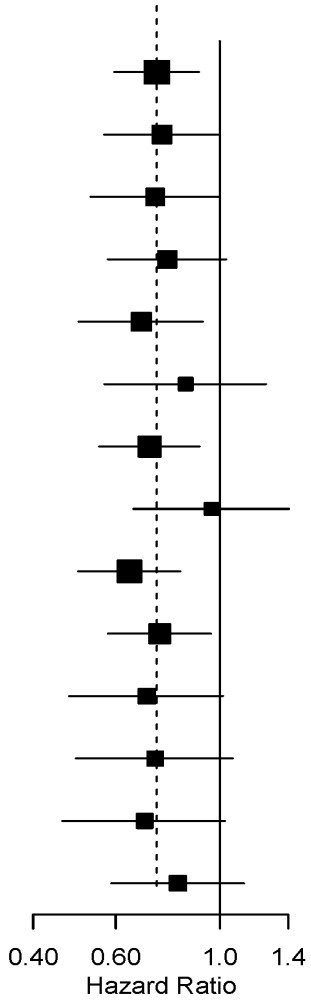
All-cause Mortality Experience in the Six Pre-specified Subgroups of Interest

Figure 4: All–Cause Mortality

Subgroup	Intensive	Standard	HR	Int P
Overall	155/4678 (3.31)	210/4683 (4.48)	0.73 (0.60,0.90)	
No Prior CKD	85/3348 (2.54)	115/3367 (3.42)	0.75 (0.57,1.00)	0.76
Prior CKD	70/1330 (5.26)	95/1316 (7.22)	0.73 (0.53,1.00)	
Age < 75	82/3361 (2.44)	104/3364 (3.09)	0.77 (0.58,1.03)	0.58
Age ≥ 75	73/1317 (5.54)	106/1319 (8.04)	0.68 (0.50,0.92)	
Female	46/1684 (2.73)	54/1648 (3.28)	0.85 (0.57,1.26)	0.49
Male	109/2994 (3.64)	156/3035 (5.14)	0.71 (0.55,0.91)	*
African–American	53/1454 (3.65)	55/1493 (3.68)	0.96 (0.65,1.40)	0.06
Non African–American	102/3224 (3.16)	155/3190 (4.86)	0.64 (0.50,0.82)	
No Prior CVD	106/3738 (2.84)	140/3746 (3.74)	0.75 (0.58,0.96)	0.78
Prior CVD	49/940 (5.21)	70/937 (7.47)	0.70 (0.48,1.02)	
SBP ≤ 132	46/1583 (2.91)	64/1553 (4.12)	0.73 (0.49,1.07)	0.70
132 < SBP < 145	41/1489 (2.75)	63/1549 (4.07)	0.69 (0.46,1.03)	
SBP ≥ 145	68/1606 (4.23)	83/1581 (5.25)	0.81 (0.59,1.13)	



p=0.34, after Hommel adjustment for multiple comparisons

Renal Disease Outcomes

		Intensive		Standard			
		Events	%/yr	Events	%/yr	HR (95% CI)	P
Participants with CKD at Baseline							
	Primary CKD outcome	**14**	**0.33**	**15**	**0.36**	**0.89 (0.42, 1.87)**	**0.76**
	≥50% reduction in eGFR*	10	0.23	11	0.26	0.87 (0.36, 2.07)	0.75
	Dialysis	6	0.14	10	0.24	0.57 (0.19, 1.54)	0.27
	Kidney transplant	0	-	0	-	-	.
	Secondary CKD Outcome						
	Incident albuminuria**	49	3.02	59	3.90	0.72 (0.48, 1.07)	0.11
Participants without CKD at Baseline							
	Secondary CKD outcomes						
	≥30% reduction in eGFR*	127	1.21	37	0.35	3.48 (2.44, 5.10)	<.0001
	Incident albuminuria**	110	2.00	135	2.41	0.81 (0.63, 1.04)	0.10

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*Confirmed on a second occasion ≥90 days apart **Doubling of urinary albumin/creatinine ratio from <10 to >10 mg/g

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.

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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)

Summary and Conclusions

- *SPRINT examined effects of more intensive antihypertensive therapy than currently recommended*
- *Participants were US adults ≥50 years with hypertension and additional risk for CVD*
- *Rapid and sustained difference in SBP achieved between the two treatment arms*
- *Trial stopped early, due to benefit, after median follow-up of 3.26 years*
- *Incidence of primary outcome (composite of CVD events) 25% lower in Intensive compared to Standard Group and all-cause mortality reduced by 27%.*
- *Treatment effect similar in all six pre-specified groups of interest.*
- *The "number needed to treat" to prevent primary outcome event or death 61 and 90, respectively*

Summary and Conclusions

- *In participants with CKD at baseline, no differences in renal outcomes*
- *In participants without CKD at baseline, incidence of eGFR reduction ≥ 30% more common in Intensive Group*
- *No overall difference in serious adverse events (SAEs) between treatment groups*
- *SAEs associated with hypotension, syncope, electrolyte abnormalities, and hospital discharge reports of acute kidney injury or acute renal failure more common in Intensive Group*
- *Overall, benefits of more intensive BP lowering exceeded the potential for harm*

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Acknowledgements

- *9,361 volunteers who agreed to participate in SPRINT*

- *Investigators and staff, including Steering Committee, other principals at the 5 Clinical Center Networks, 102 participating Clinical Centers, Coordinating Center, Central Laboratory, ECG Reading Center, MRI Reading Center, and Drug Distribution Center*

- *National Institutes of Health*
  - *National Heart, Lung, and Blood Institute (NHLBI)*
  - *National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)*
  - *National Institute on Aging (NIA)*
  - *National Institute of Neurological Disorders and Stroke (NINDS)*

- *SPRINT Data and Safety Monitoring Board (DSMB)*

- *Takeda and Arbor Pharmaceuticals (donated 5% of medication used)*

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Thank You

Additional details of the SPRINT principal results

The SPRINT Research Group
A Randomized Trial of Intensive versus Standard Blood-Pressure Control
N Engl J Med. DOI: 10.1056/NEJMoa 1511939
(simultaneous e publication)

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SPRINT Timeline

- *Planning: September 2009*
- *Start Recruitment: November 2010*
- *End Recruitment: March 2013*
- *Intervention Stopped: August 2015*
- *Announcement of Preliminary Main Results: September 2015*
- *Presentation & Publication of Main Results: November 2015*
- *Anticipated Completion of Close-out Visits: 2016*