Systolic Blood Pressure Intervention Trial (SPRINT)

IN **A NEPHROLOGIST'S** VIEW

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Current guidelines for BP control

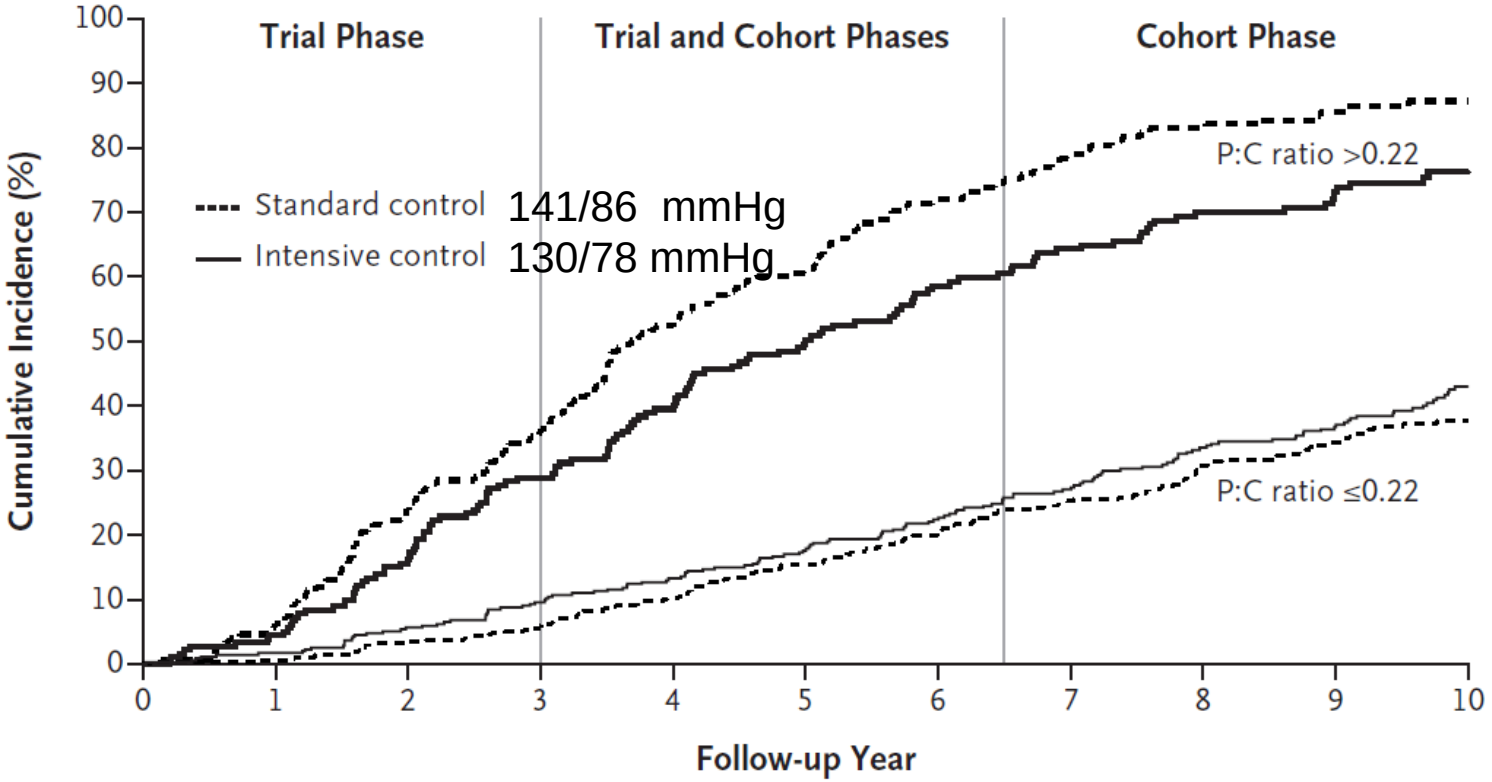
- Lowering BP < 130/80mmHg in high-risk patients (**diabetes** or a history of **CV or renal disease**) is **not** supported by **RCT evidence.**
- In **diabetes**, HOT, UKPDS trials showing benefits from **DBP** reductions to between **80–85 mmHg.**

- **Target BP in diabetes: 140/85 (ESC, KSH)**
- What about **JNC VIII: 140/90**

Previous evidence for CKD

- In **non-DM CKD (MDRD, AASK, REIN2),** lower target BP (125–130mmHg) showed **no differences** in ESRD or death c/w (<140mmHg)
  - **Only a prolonged observational follow-up study** showed a beneficial trend in patients with **proteinuria**
- In ACCORD trial with baseline eGFR in the normal range, **more intensive lowering of BP** (119/67 vs. 134/73mmHg) associated with a **near-doubling of cases with eGFR < 30 ml/min/1.73m^2**

Intensive Blood Pressure Control in **Hypertensive** Chronic Kidney Disease



P:C Ratio >0.22											
Standard control	176	165	134	113	81	66	45	32	26	22	13
Intensive control	181	172	151	128	109	87	67	56	47	40	25
P:C Ratio ≤0.22											
Standard control	376	373	362	353	332	302	267	234	214	196	128
Intensive control	357	350	335	321	306	282	254	228	206	189	128

African American study of kidney disease N = 1094 *N Engl J Med 2010;363:918-929*

HT management in CKD

KDIGO 2012 guideline

Albuminuria	BP target	Preferred agent	
< 30 mg/day	≤ 140/90 mmHg	None	**1B**
30-300 mg/day	≤ 130/80 mmHg	ACEI or ARB	**2D**
> 300mg/day	≤ 130/80 mmHg	ACEI or ARB	**2C**

- **ESC**: patients with diabetic or non-diabetic CKD: **< 140/90 mmHg (IIa)**
  - –For subjects with proteinuria: SBP < 130mmHg (**IIb)**
- **JNC VIII**: **140/90 regardless of proteinuria**

Kidney Int 2012;2(Suppl):337-414

2013 대한고혈압학회 진료지침 요약본

2.3 목표혈압

상황	수축기혈압(mmHg)	확장기혈압(mmHg)
단순고혈압	140	90
고령 고혈압	140~150	90
당뇨병	140	85
뇌졸중	140	90
관상동맥질환	140	90
만성콩팥병		
알부민뇨(–)	140	90
알부민뇨(+)*	130	80

* 알부민뇨, 24시간뇨 알부민 > 30 mg/day 혹은 임의뇨 알부민:크레아티닌 비 > 30 mg/g (3 mg/mmol)

SPRINT Research Question

Examine effect of more intensive high blood pressur e 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.***

- ***≥50 years old***
- ***SBP 130 – 180 mm Hg (treated or untreated)***
  1. SBP: 130 – 180 mm Hg on 0 or 1 medication
  2. SBP: 130 – 170 mm Hg on up to 2 medications
  3. SBP: 130 – 160 mm Hg on up to 3 medications
  4. SBP: 130 – 150 mm Hg on up to 4 medications
- ***Additional CVD risk At least one***

Age ≥ 75 years
Clinical or subclinical CVD (excluding stroke)
CKD (eGFR 20 – <60 ml/min/1.73m^2)
Framingham Risk Score for 10-year CVD risk ≥ 15%

Screened (N=14,692)

*Stroke, DM, **PKD,** CHF (symptoms or EF < 35%)*

PU >1g/d, eGFR < 20 mL/min/1.73m^2 (MDRD)

Adherence concerns

Randomized (N=9,361)

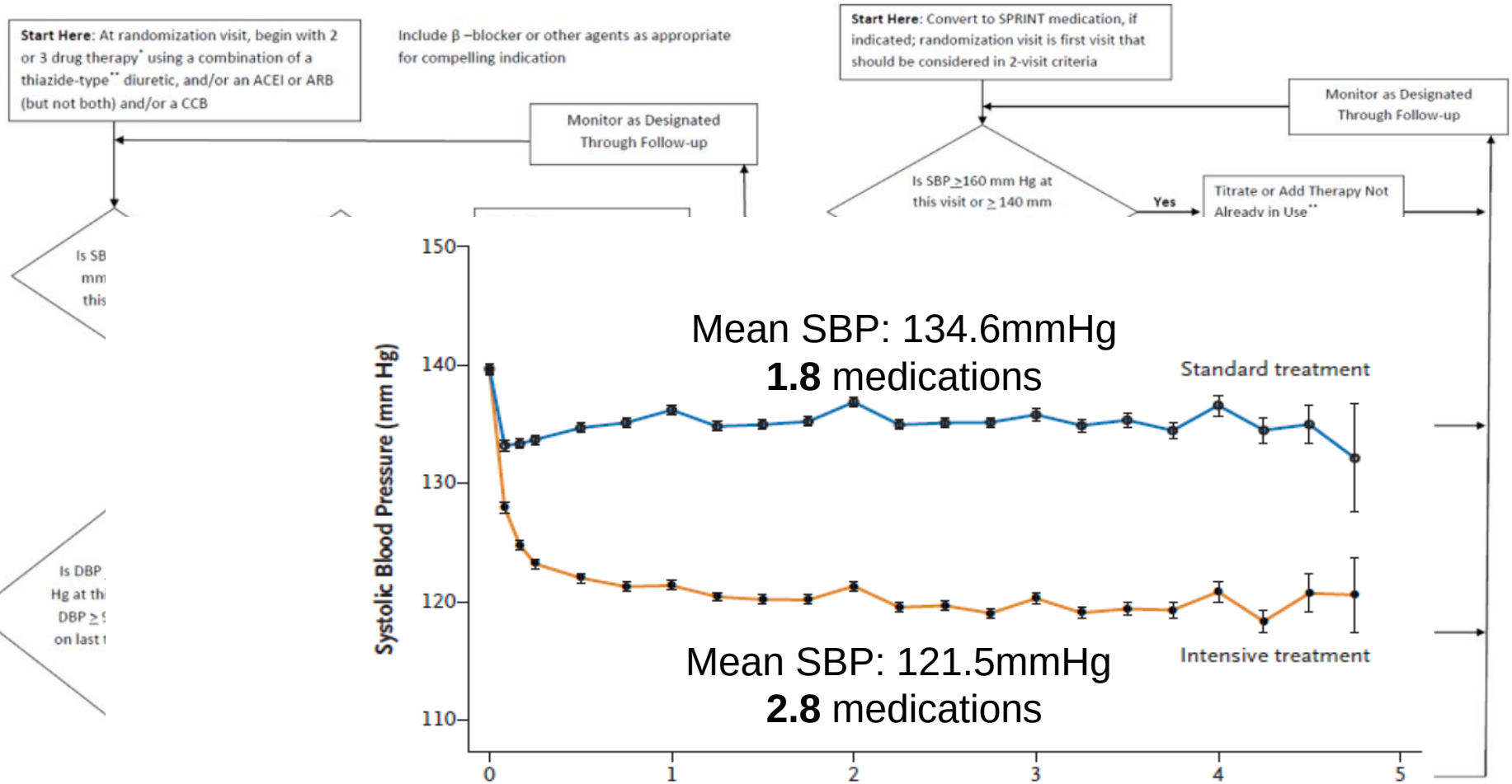
	SBP < 120 mm Hg	***SBP < 140 mm Hg***
	Intensive Treatment (N=4,678)	***Standard Treatment (N=4,683)***
• Consent withdrawn	224	242
• Discontinued intervention	111	134
• Lost to follow-up	154	121
Analyzed (ITT)	***4,678***	***4,683***

N Engl J Med 2015;373(22):2103-2116

Baseline Characteristics

	Total N=9361	Intensive N=4678	Standard N=4683
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%
Prior CVD, %	20.1%	20.1%	20.0%
10-year Framingham CVD risk, %	20.1%	20.1%	20.1%
Taking antihypertensive meds, %	90.6%	90.8%	90.4%
Number of antihypertensive meds	1.8 (1.0)	2.8 (1.0)	1.8 (1.0)
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)
eGFR, mL/min/1.73 m²	**71.7 (20.6)**	**71.8 (20.7)**	**71.7 (20.5)**
% with eGFR < 60 mL/min/1.73m²	**28.3**	28.4	28.1
Urine albumin/creatinine, mg/g	**42.6 (166.3)**	**44.1 (178.7)**	**41.1 (152.9)**

Intensive vs. standard arm



No. with Data										
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286
Mean No. of Medications										
Standard treatment	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9
Intensive treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8	2.8	2.8	3.0

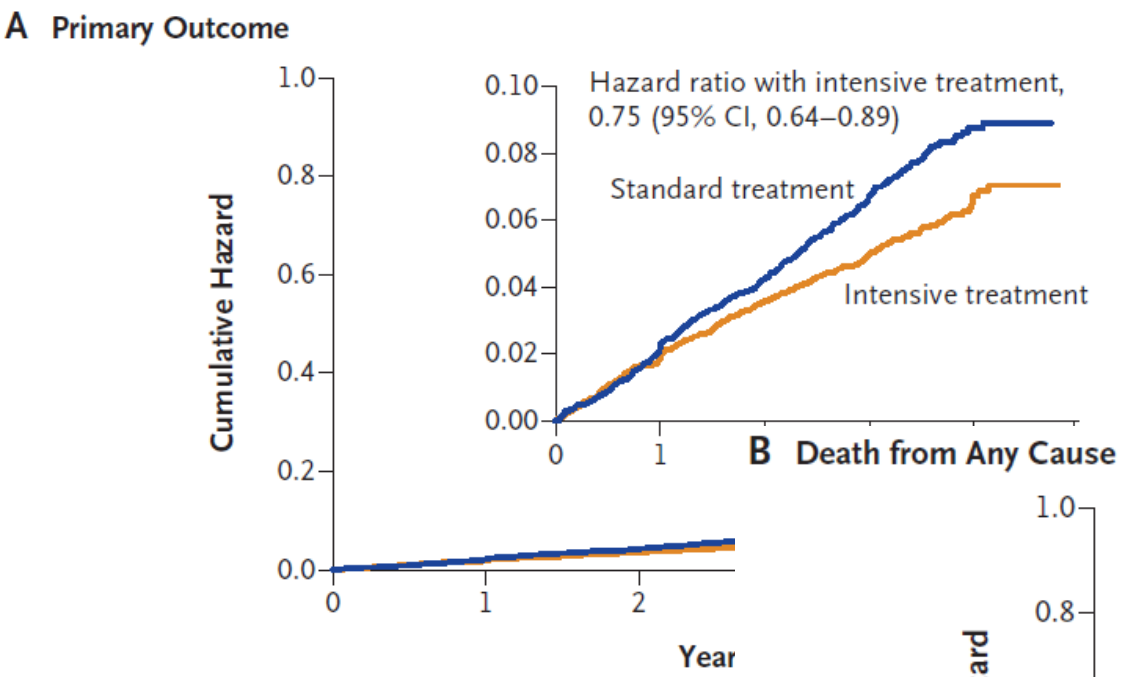
Primary Hypothesis and outcomes

- ***CVD composite event rate*** *lower in intensive (vs. standard)*
- ***Primary outcomes: MI; non-MI ACS; Stroke; ADHF; CVD***

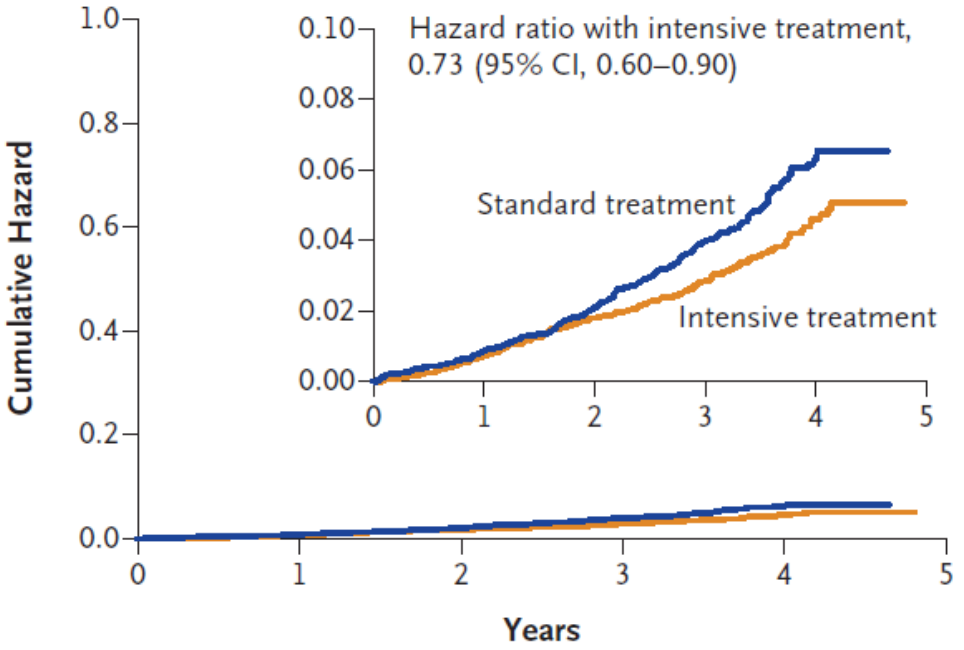
****Estimated power of 88.7% to detect a 20% difference (n=9,250)***

→ 4-6 years of follow-up and loss to follow-up of 2%/year.

- *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****)*



No. at Risk			
Standard treatment	4683	4437	4228
Intensive treatment	4678	4436	4256



No. at Risk					
Standard treatment	4683	4528	4383	2998	789
Intensive treatment	4678	4516	4390	3016	807

- ***Primary outcomes***
  - ***CVD composite: first occurrence of MI; non-MI ACS; Stroke; Acute decompensated HF; CVD death (NO ESRD)***

Primary Outcome and its Components

	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

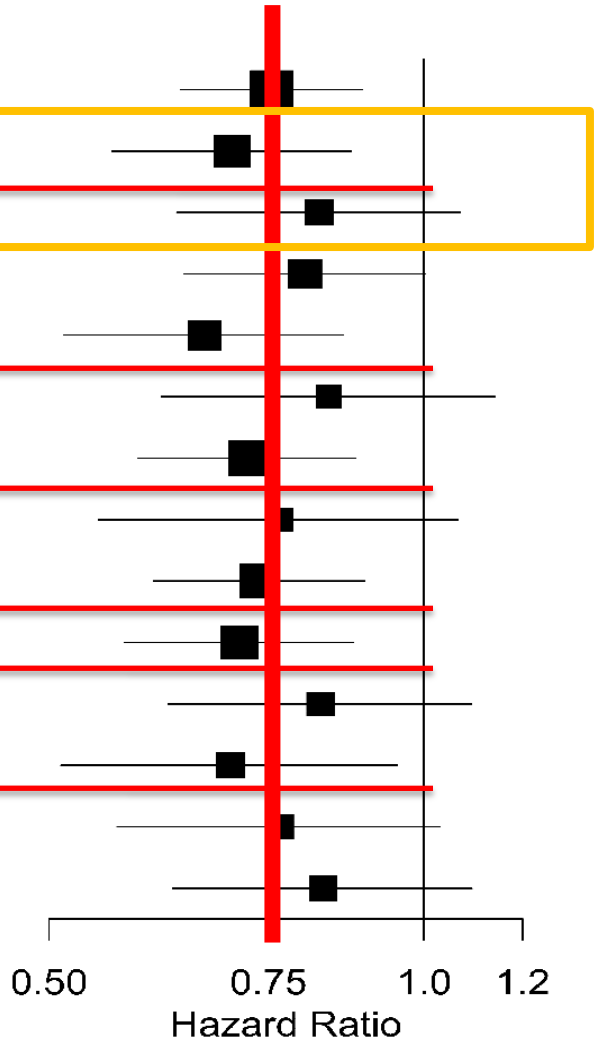
Cause of death in the SPRINT trial

Cause of death	Overall	Intensive	Standard
CVD Death	102	37	65
__CHD Death	50	18	32
__Stroke	17	8	9
__Sudden cardiac death	13	2	11
__CHF	17	8	9
__Not cardiac but other cardiovascular	5	1	4
Non-CVD Death	192	90	102
__Death from kidney disease	2	1	1
__Death related to dialysis procedure	1	0	1
__Other cardiac/non-ischemic	2	0	2
__Cancer	101	49	52
__Accident/Injury/Suicide/Homocide	14	4	10
__Other noncardiac, nonstroke death	72	36	36
Undetermined	71	28	43
__Unclassifiable	35	13	22
__Not yet adjudicated	36	15	21
Total	365	155	210

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

	Subgroup	HR	P*
	Overall	0.75 (0.64,0.89)	
1	No Prior CKD	0.70 (0.56,0.87)	0.36
	Prior CKD	0.82 (0.63,1.07)	
2	Age < 75	0.80 (0.64,1.00)	0.32
	Age ≥ 75	0.67 (0.51,0.86)	
3	Female	0.84 (0.62,1.14)	0.45
	Male	0.72 (0.59,0.88)	
4	African−American	0.77 (0.55,1.06)	0.83
	Non African−American	0.74 (0.61,0.90)	
5	No Prior CVD	0.71 (0.57,0.88)	0.39
	Prior CVD	0.83 (0.62,1.09)	
6	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)	

*Unadjusted for multiplicity



Renal Outcomes

- ***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/1.73m²)***
  - ***Participants with or without CKD at baseline: Incidence of albuminuria , Doubling of urinary albumin/creatinine (<10 to >10 mg/g)***

Renal outcome

Outcome	Intensive treatment		Standard treatment		HR(95% CI)	P Value
	Patients(%)	% per year	Patients(%)	% per year		
CKD	**(N = 1330)**		**(N=1316)**			
Composite renal outcome	**14(1.1)**	0.33	**15(1.1)**	0.36	0.89(0.42-1.87)	0.76
≥ 50% reduction of eGFR	**10(0.8)**	0.23	**11(0.8)**	0.26	0.87(0.36-2.07)	0.75
Dialysis	**6(0.5)**	0.14	**10(0.8)**	0.24	0.57(0.19-1.54)	0.27
KT	0		0			
Incident albuminuria	49/526(9.3)	3.02	59/500(11.8)	3.90	0.72(0.48-1.07)	0.11
W/O CKD	**(N=3332)**		**(N=3345)**			
≥ 30% reduction in eGFR to < 60ml/min	**127(3.8)**	**1.21**	**37(1.1)**	**0.35**	**3.49(2.44-5.10)**	**< 0.001**
Incident albuminuria	110/1769(6.2)	2.00	135/1831(7.4)	2.41	0.81(0.63-1.04)	0.10

- ***CKD at baseline: incidence of decline in eGFR ≥50% or ESRD***
- ***no CKD at baseline: incidence of decline in eGFR ≥30% & to <60 mL/min/1.73m²***
- ***Incidence of albuminuria; Doubling of urinary albumin/creatinine (<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)

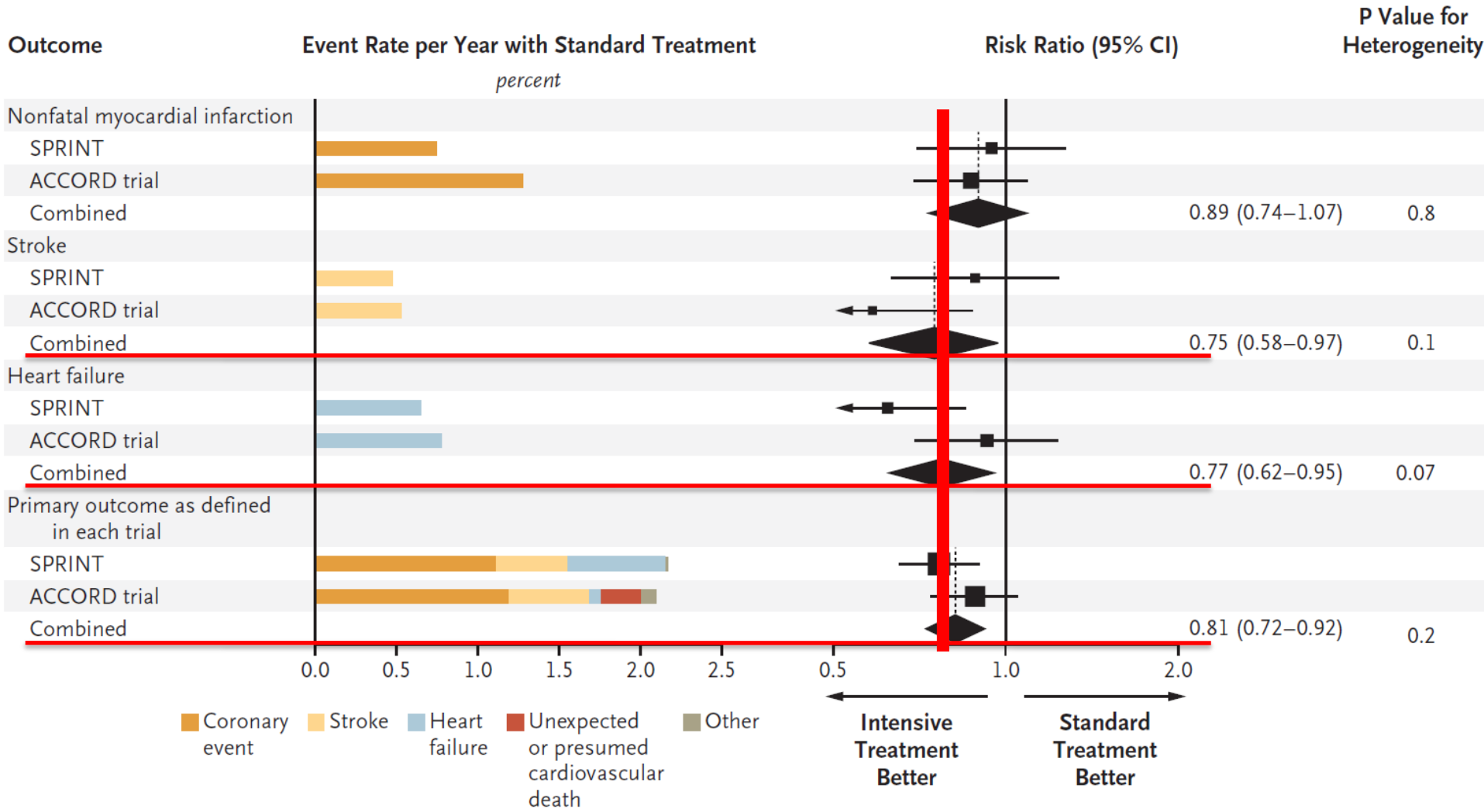
**Fatal or life threatening event, resulting in significant or persistent disability, requiring or prolonging hospitalization, or judged important medical event.*

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)*

Combined analysis (SPRINT + ACCORD)



Diabetes, Age (62 vs 68), Cr < 1.5 mg/dL, Sample size (4733 vs 9361), factorial design

N Engl J Med. 2015 Nov 26;373(22):2175-8

Summary of SPRINT

- *Participants, US adults ≥50 years with HT 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 effects,* ***similar in all six pre-specified groups*** *of interest.*
- *The "****number needed to treat****" to prevent primary outcome event , death, CVD death 61, 90 and* ***172*** *respectively*

Summary of SPRINT

- *CKD at baseline,* ***no differences*** *in renal outcomes*
- *No 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,* ***more common in Intensive Group***

No changes in target BP for

- **Diabetes**
- Previous **stroke**
- Hypertensive subjects **under** the age of 50
- **Low risk** **hypertensives** without history of CHD or CKD with framingham risk score less than 15
- CKD with **overt proteinuria (PU > 1g/day)**

SBP target can be lowered to below 130mmHg if tolerated for

- Patients over the age of 50 with **previous CHD**
- **High risk** **hypertensives** over the age of 50
- **Non frail elderly** hypertensives
- **Non diabetic CKD** without overt proteinuria

1 additional medication for 172 subjects

to reduce 1 CVD mortality

Managing Hypertension in Patients with CKD: A Marathon, Not a SPRINT

- 1. ALERT: **SPRINT IS NOT A TYPICAL CKD TRIAL**
  - **Renal outcomes were not primary**
  - ***Advanced CKD or significant proteinuria ?***
- **2. CAVEAT**
  - **At high risk for death and cardiovascular events**
  - ***Lower event rates in Lower risk population ?***
- ***3. Present action and future direction***
  - Determining the optimal BP targets for all patients with CKD will likely take one to two decades of effort: a marathon, not a sprint.

A SPRINT to the finish, or just the beginning? Implications of the SPRINT results for nephrologists

- CV events and all cause mortality **outweights** the risk of AKI (in a very small proportion of participants)
- At least 1 additional antihypertensive agent
  - To minimize **the risk of AKI, eGFR should be monitored** after the addition of an antihypertensive agent/ an increase in dose of an existing antihypertensive agent
- Gradual escalation of treatment with close attention to adverse events related treatment
  - **electrolyte** disorders, acute deterioration in **kidney** function, orthostatic **hypotension** and drug side effects

HT management in CKD

Albuminuria	BP target	Preferred agent	
< 30 mg/day	≤ 140/90 mmHg	None	1B
→ **High risk hypertensives: Low SBP target (high level of evidence)**			
30-300 mg/day	**≤ 130/80 mmHg**	ACEI or ARB	2D
→ **Non diabetec CKD: Low SBP target (high level of evidence)**			
> 300mg/day	≤ 130/80 mmHg	ACEI or ARB	2C
→ **Non diabetec CKD (< 1g/day): Low SBP target (high level of evidence)**			