Insights from Systolic Blood Pressure Intervention Trial(SPRINT): Hypertension specialist's view

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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.***

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/1.73m²*
  - *Framingham Risk Score for 10-year CVD risk ≥ 15%*
  - *Age ≥ 75 years*

At least one

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

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Systolic Blood Pressure Intervention Trial

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*
- *Hypertensive patients under the age of 50*

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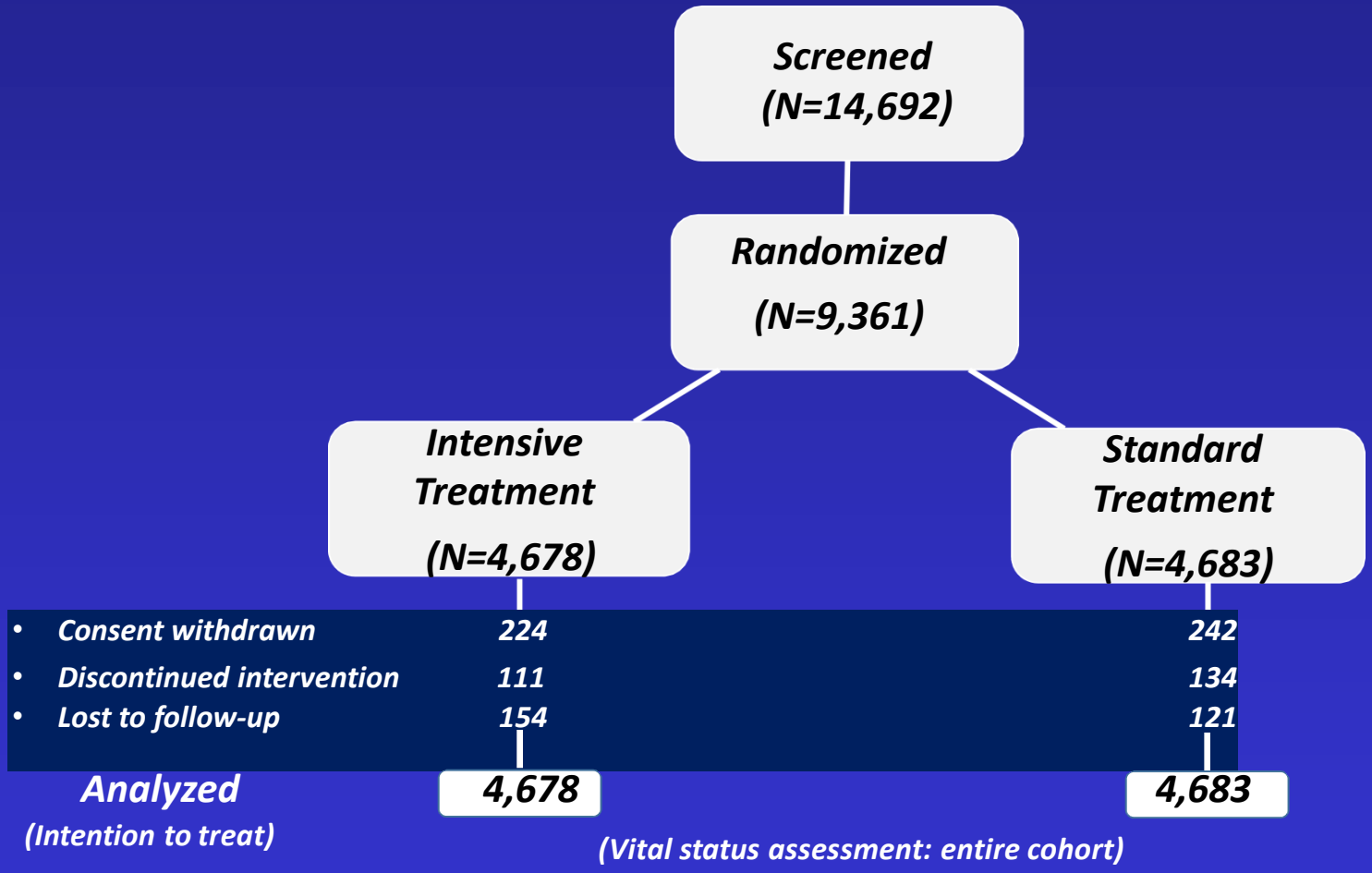
SPRINT: Enrollment and Follow-up Experience



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

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)	2.8 (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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	Intensive (N=4678)	*Standard (N=4683)*
Number of agents		
Average	2.7 (1.2)	1.8 (1.1)
0	125 (2.7)	530 (11.3)
1	493 (10.5)	1455 (31.1)
2	1429 (30.5)	1559 (33.3)
3	1486 (31.8)	807 (17.2)
4+	1137 (24.3)	323 (6.9)
ACE-I or angiotensin II antagonist	3580 (76.7)	2582 (55.2)
ACE inhibitors	1729 (37.0)	1320 (28.2)
Angiotensin II antagonists	1854 (39.7)	1264 (27.0)
Renin inhibitors	1 (0.0)	1 (0.0)
Diuretics	3127 (67.0)	2006 (42.9)
Thiazide-type diuretics	2562 (54.9)	1557 (33.3)
Aldosterone receptor blockers	405 (8.7)	185 (4.0)
Other potassium-sparing diuretics	144 (3.1)	119 (2.5)
Alpha-1 blockers	482 (10.3)	258 (5.5)
Beta blockers	1919 (41.1)	1440 (30.8)
With intrinsic sympathomimetic activity	0 (0.0)	0 (0.0)
Without intrinsic sympathomimetic activity	1919 (41.1)	1440 (30.8)
Central alpha-2 agonists or other centrally acting drugs	107 (2.3)	44 (0.9)
Calcium channel blockers	2667 (57.1)	1654 (35.4)
Dihydropyridines	2465 (52.8)	1463 (31.3)
Non-dihydropyridines	218 (4.7)	199 (4.3)
Direct vasodilators	340 (7.3)	110 (2.4)

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)

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

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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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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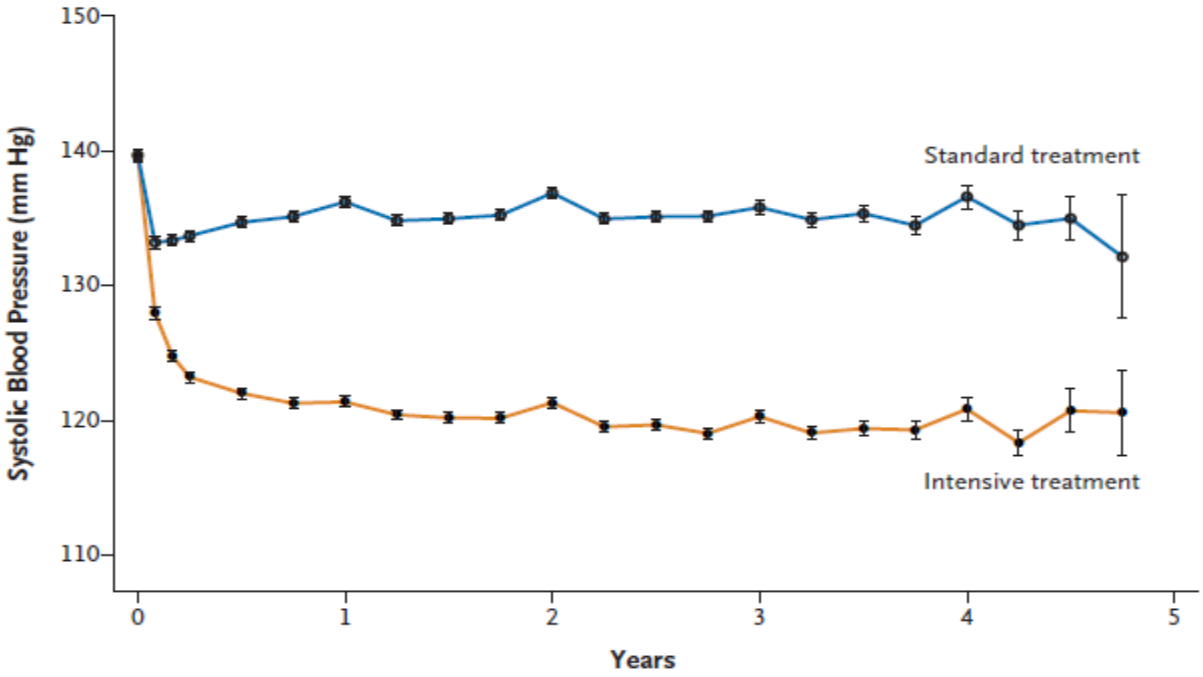
Systolic Blood Pressure Intervention Trial

Achieved BP reduction

Mean SBP: 121.5mmHg in intensive treatment arm
Mean SBP: 134.6mmHg in standard treatment 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

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Blood Pressure Measurement in SPRINT

- Blood pressure readings were conducted in a **unique manner that is probably not the standard in our office.**
- Patients were asked to sit quietly for 5 minutes before blood pressure was measured by an automated unit(**OMRON HEM 907**).
- Three readings were obtained over several minutes with **no clinician or nurse** in the room.

Conventional versus automated measurement of blood pressure in primary care patients with systolic hypertension: randomised parallel design controlled trial

Martin G Myers, professor of medicine,[1] Marshall Godwin, professor of medicine,[2] Martin Dawes, professor of medicine,[3] Alexander Kiss, assistant professor,[4] Sheldon W Tobe, associate professor of medicine,[5] F Curry Grant, director,[6] Janusz Kaczorowski, professor of medicine[7]

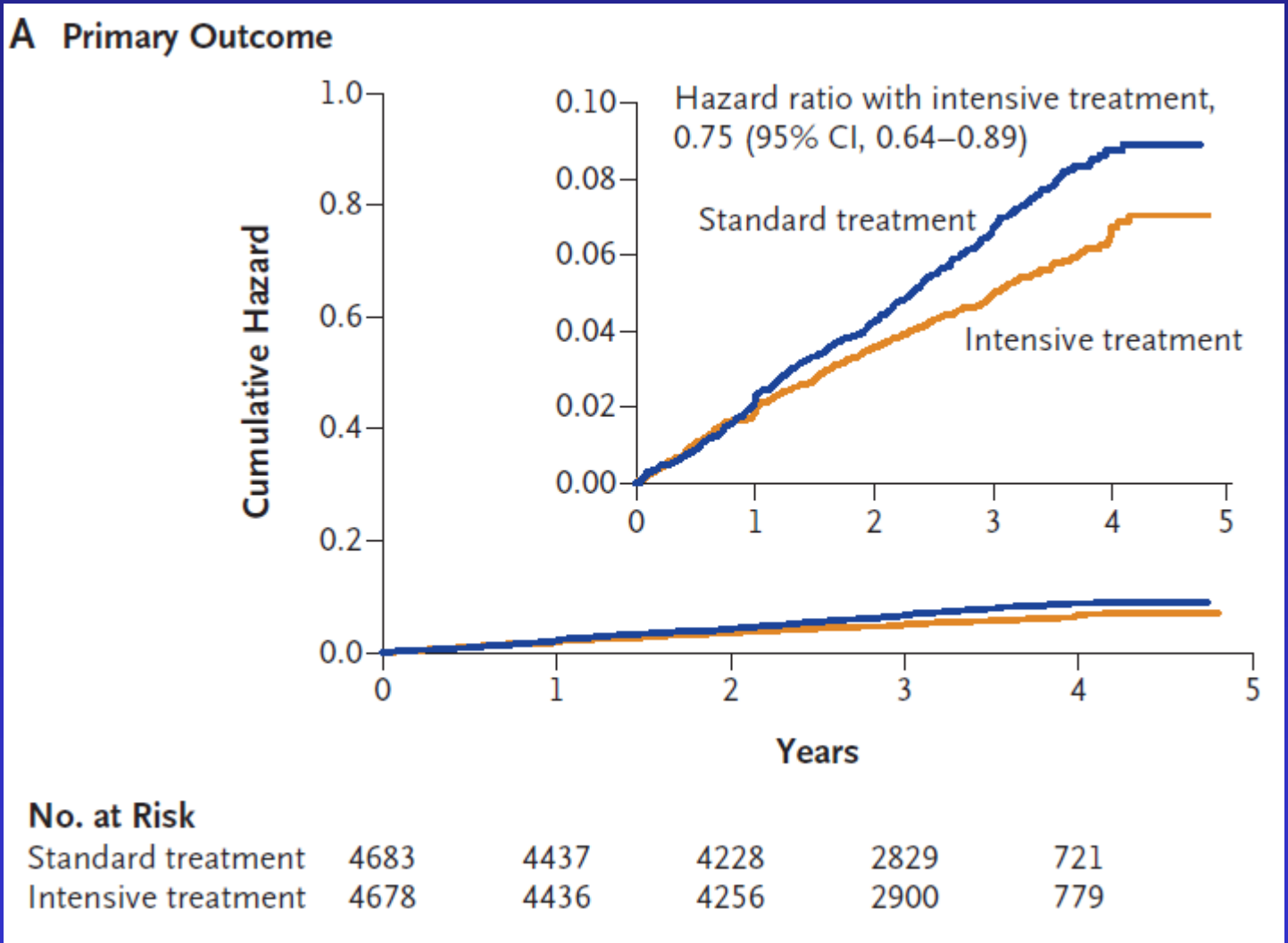
CAMBO trial. BMJ 2011;342:d286

Measurement	Automated office BP group (n=299)	Conventional manual office BP group (n=249)
Last routine manual office BP (mm Hg)	149.5 (10.8)/81.4 (8.3)	149.9 (10.7)/81.8 (8.5)
Office BP (mm Hg) after enrolment	135.6 (17.3)/77.7 (10.9)	141.4 (14.6)/80.2 (9.5)
Difference from last routine office BP (mm Hg)	−13.9 (−11.8 to −16.1)***/−3.7 (−2.5 to −4.8)***	−8.5 (−6.5 to −10.4)***/−1.6 (−0.4 to −2.8)**
Awake ambulatory BP (mm Hg)	133.2 (12.4)/74.4 (9.8)	135.0 (13.1)/75.9 (10.0)
Difference from last routine office BP (mm Hg)	−16.3 (−14.5 to −18.1)***/−7.0 (−5.8 to 8.1)***	−14.9 (−12.9 to −17.0)***/−5.9 (−4.6 to 7.2)***
Difference from post-enrolment office BP (mm Hg)	−2.3 (−0.31 to −4.3)*/−3.3 (−2.2 to −4.4)***	−6.5 (−4.3 to −8.6)***/−4.3 (−2.9 to 5.8)***

*P=0.02.
**P=0.01.
***P<0.001.

Net reduction of BP by automated office BP: 5.4/2.1mmHg

SPRINT primary outcome



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

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

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

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

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How much should SPRINT impact the guidelines?

SPRINT not applicable for HT patients with

- 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

Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial

The SPS3 Study Group*

Lancet 2013;382:507-515

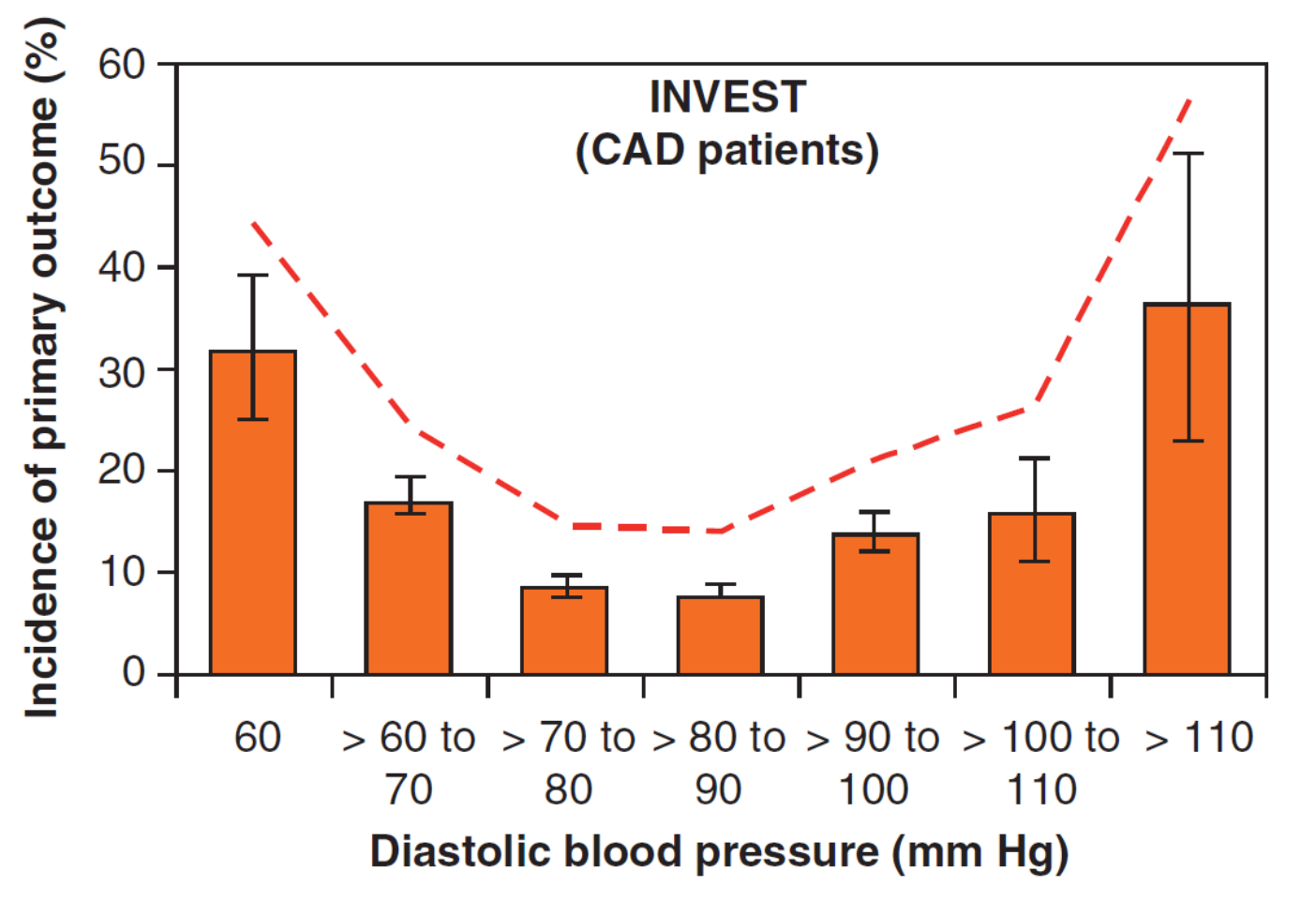
- 3020 subjects with recent lacunar infarct
- Open label: SBP < 130(127mmHg) vs SBP; 130-149(138mmHg)
- **Non significant reduction in stroke(HR: 0.81, 95 % CI: 0.64-1.03, P = 0.08)**
- Composite outcome of stroke, MI or vascular death(HR: 0.84, 0.68-1.04, P = 0.32)
- **Significant reduction of ICH(HR: 0.37, 0.15-0.95, P = 0.03)**

Issues to discuss

- Why wasn't the J curve observed in the SPRINT study?
-
- Do we start treating high risk hypertensives at SBP 130mmHg?
- What proportion of the population are eligible?
- What about diabetes?

J curve in HT patients with CAD

22,576 patients with HT and CAD



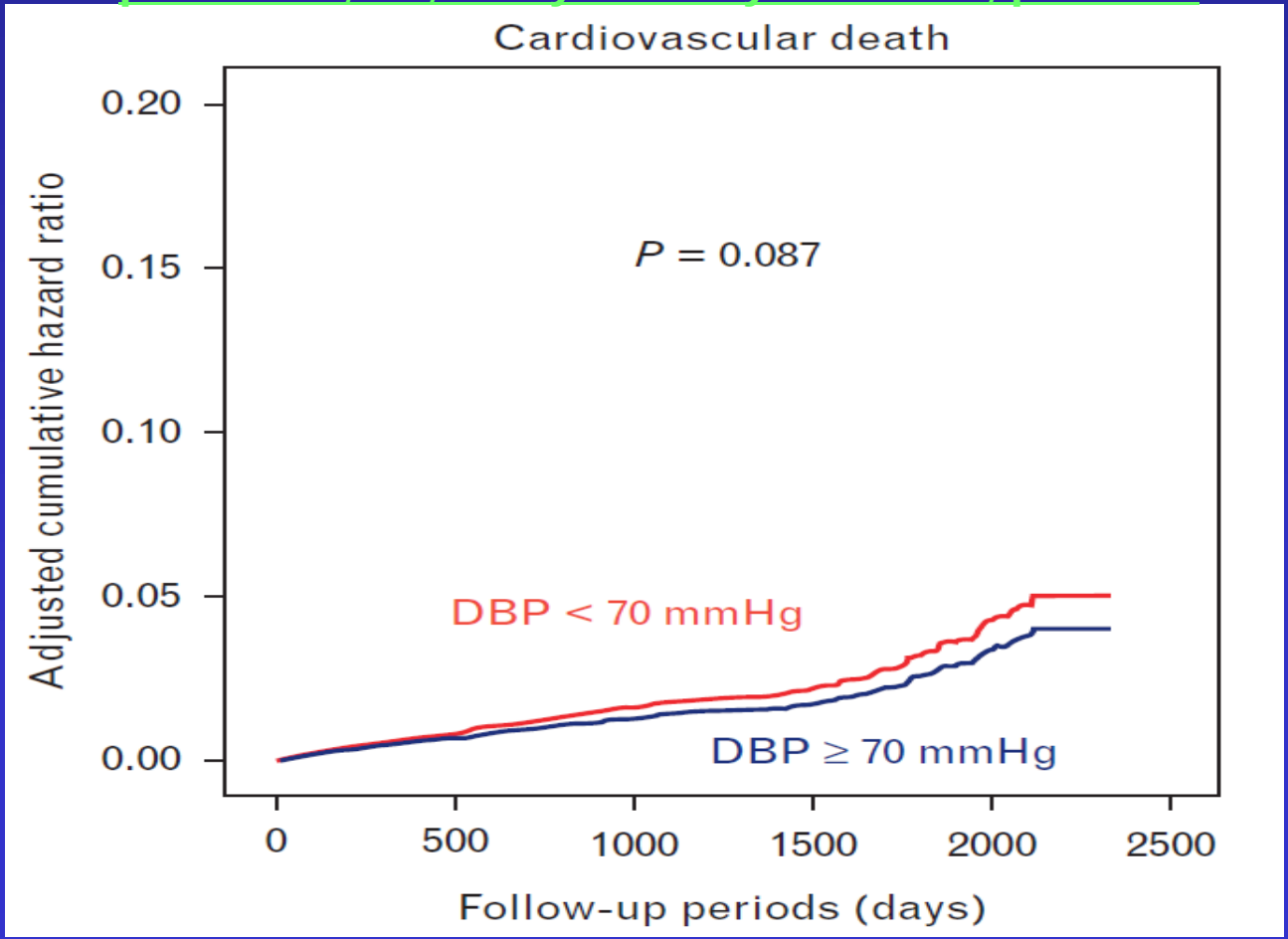
Messerli FH et al. Ann Intern Med. 2006;144:884-893.

Low DBP may not be an independent risk for cardiovascular death in revascularized coronary artery disease patients

Hisashi Kai[a], Takafumi Ueno[b], Takeshi Kimura[c], Hisashi Adachi[d], Yutaka Furukawa[e], Toru Kita[e], Tsutomu Imaizumi[a], on behalf of CREDO-Kyoto Investigators

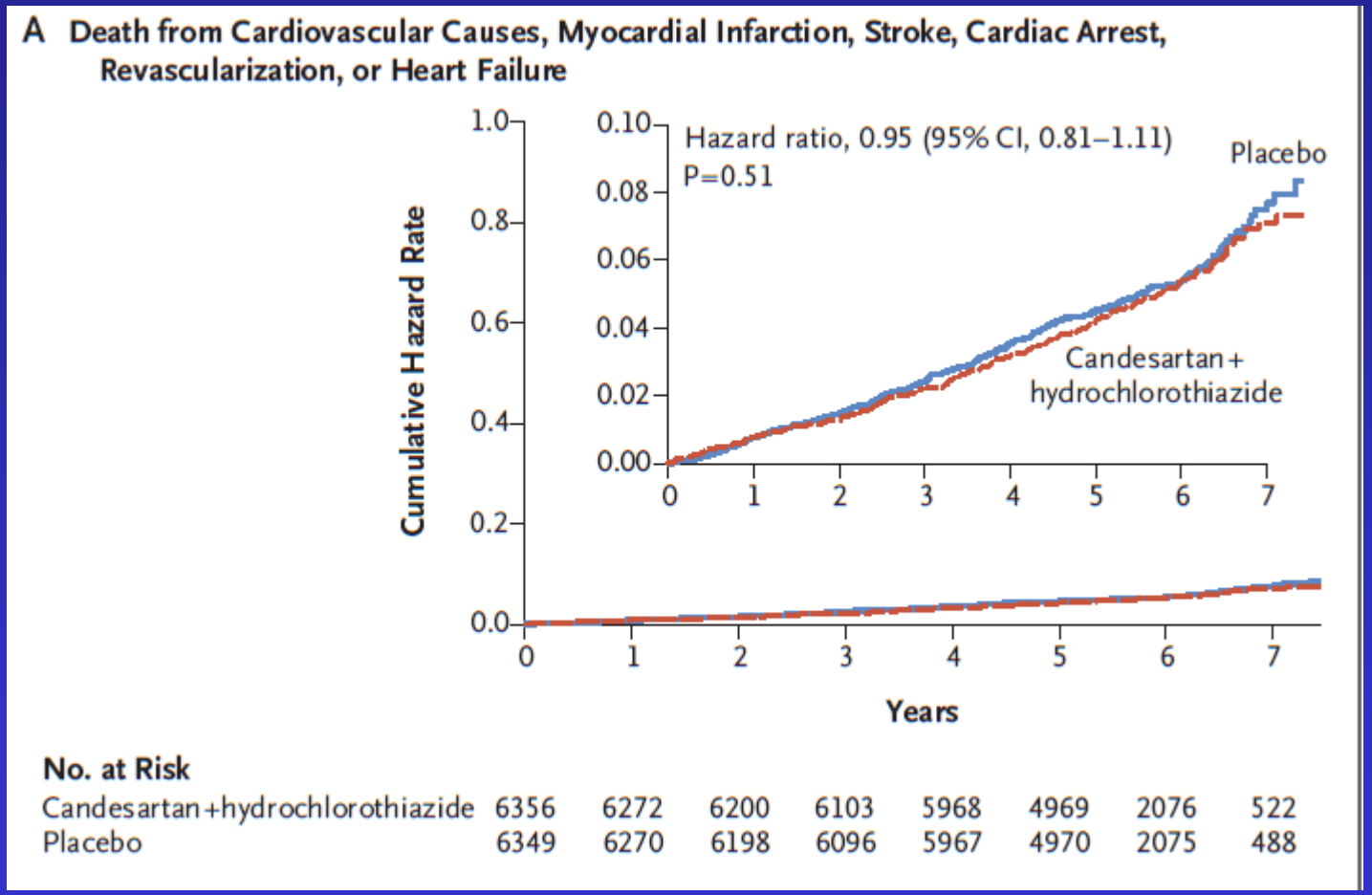
Kai H et al. J Hypertens 2011;29:1889-1896

7180 stable CAD(Median FU: 3.6 years) Adjusted for age, sex, eGFR, heart failure, prior CVD, PP, LV systolic dysfunction, prior MI



HOPE-3 trial

12,705 subjects(Median FU: 5.6 years)

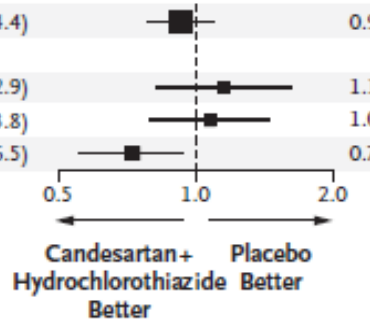


Lonn EM et al. N Engl J Med 2016 in press

HOPE-3 trial: Subgroup according to baseline BP

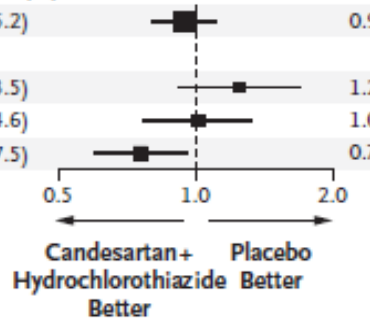
A First Coprimary Outcome

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)	



Lonn EM et al. N Engl J Med 2016 in press

Generalizability of SPRINT Results to the U.S. Adult Population

Adam P. Bress, PharmD, MS,[a] Rikki M. Tanner, PhD, MPH,[b] Rachel Hess, MD, MS,[c] Lisandro D. Colantonio, MD, MS,[b] Daichi Shimbo, MD,[d] Paul Muntner, PhD[b]

- NHANES(2007-2012)
- 7.6% of adult US population
- 16.7% of adults with treated hypertension
- 51.0% of SPRINT eligible US population not treated for hypertension

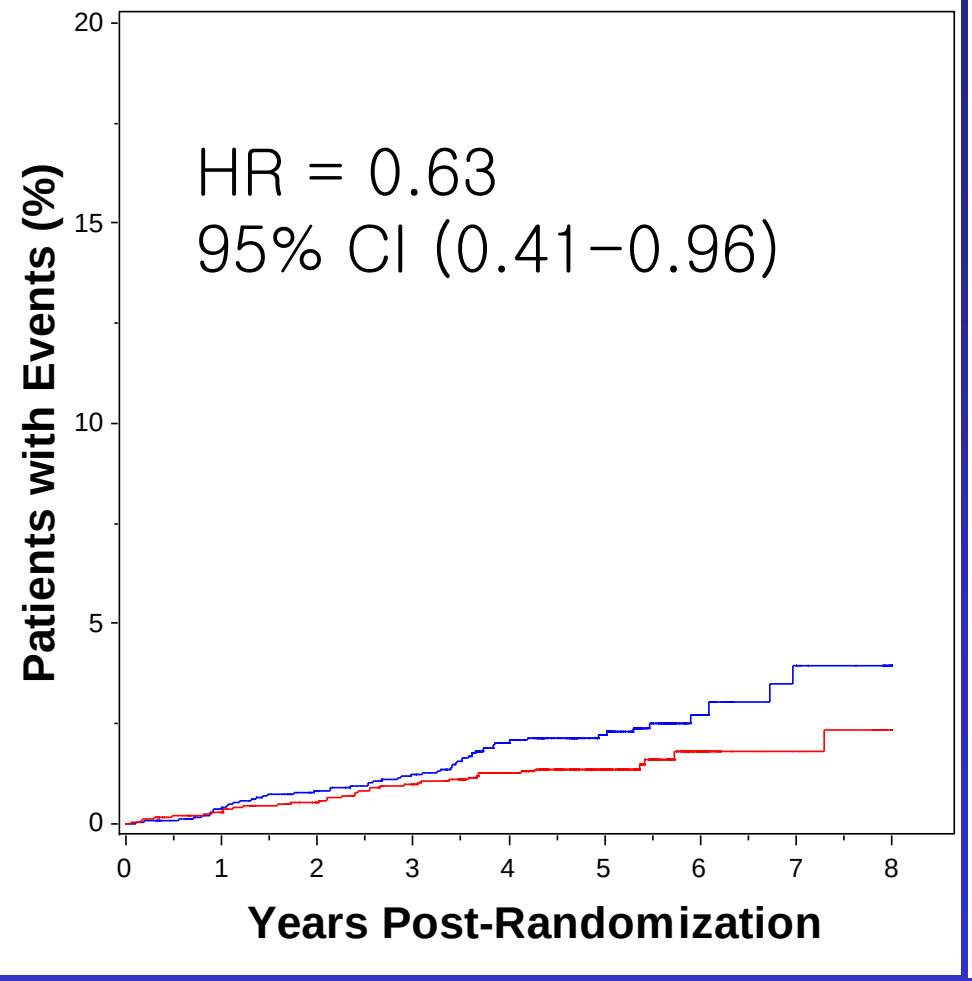
Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses

Mattias Brunström, Bo Carlberg

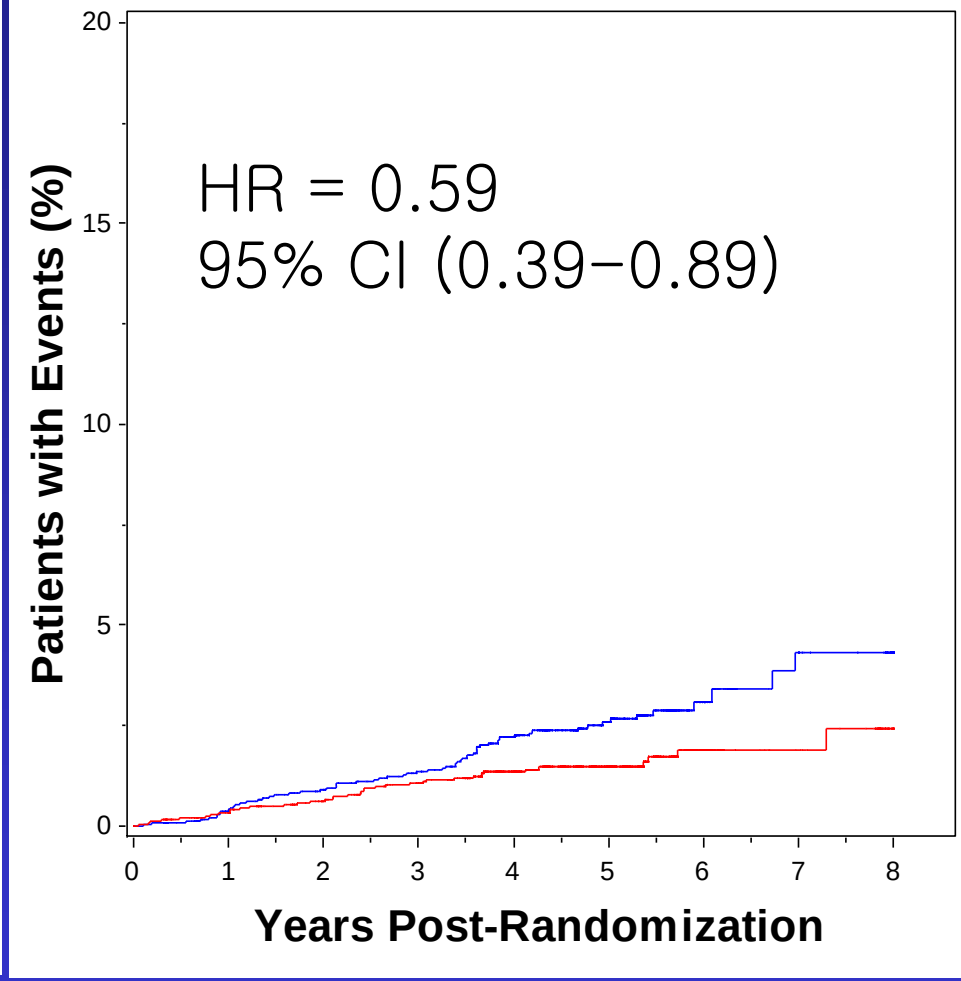
BMJ 2016;352:i717

- 49 trials, including 73738 diabetics, treated for 12 months or more
- CV mortality: reduced if baseline SBP more than 150mmHg, no effect for SBP; 140-150mmHg, CV mortality increased by 15% when baseline SBP < 140mmHg. **Tendency toward harm when achieved SBP < 130mmHg**
- CHF and MI: beneficial if baseline SBP more than 140mmHg and attained SBP more than 130mmHg. **Metaregression showed crossing to harm at SBP 132mmHg for AMI**

Nonfatal Stroke



Total Stroke



Intensive Standard

ACCORD study group. N Engl J Med 2010

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 without previous history of CHD or MI
- Non frail elderly hypertensives
- Non diabetic CKD without overt proteinuria → Extend to all CKD?
- Maybe diabetics at high risk of CVD


Thank you very much
for your attention

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)*-

SPRINT
Systolic Blood Pressure Intervention Trial

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

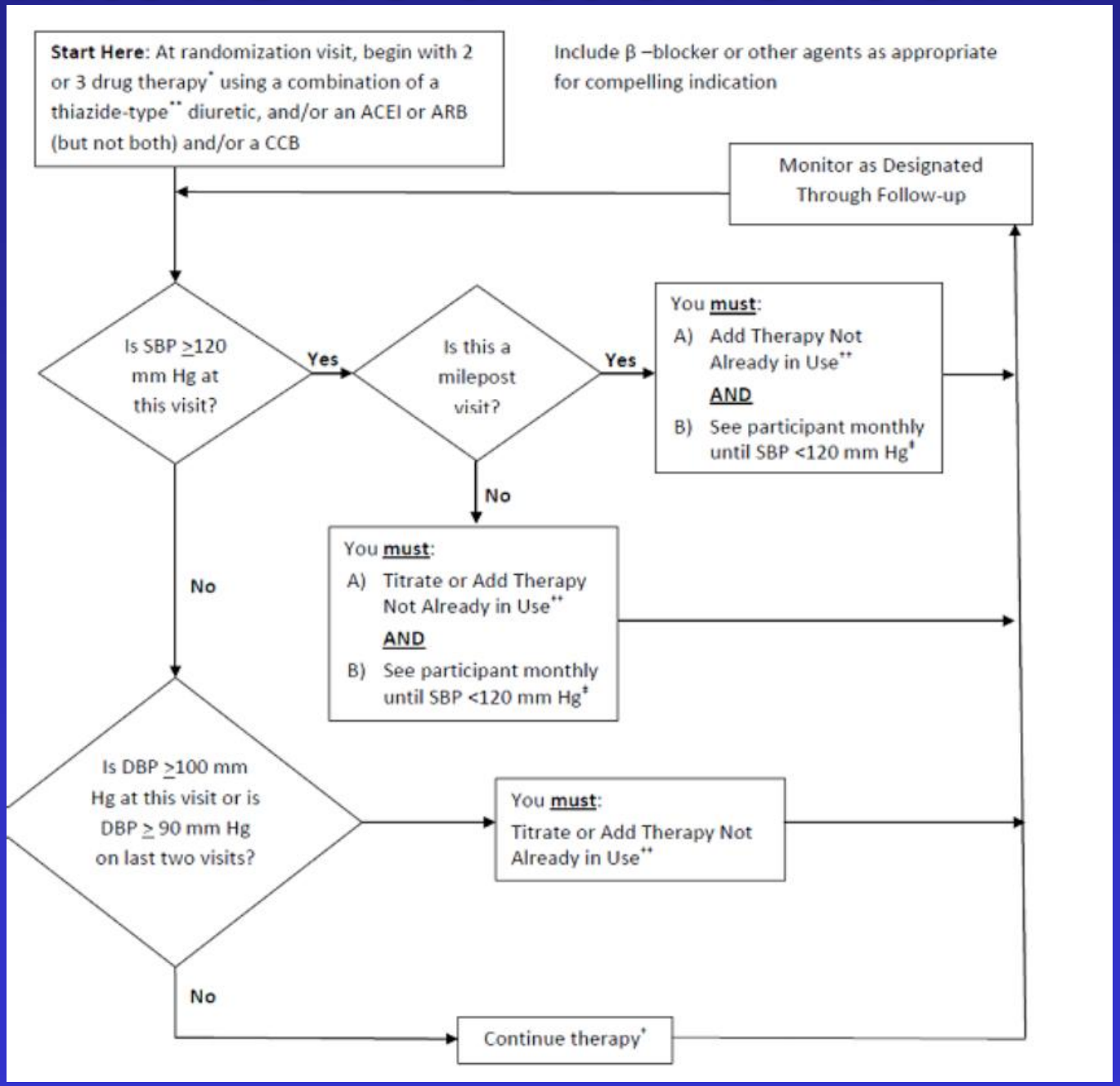
Additional Outcomes

- *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)*

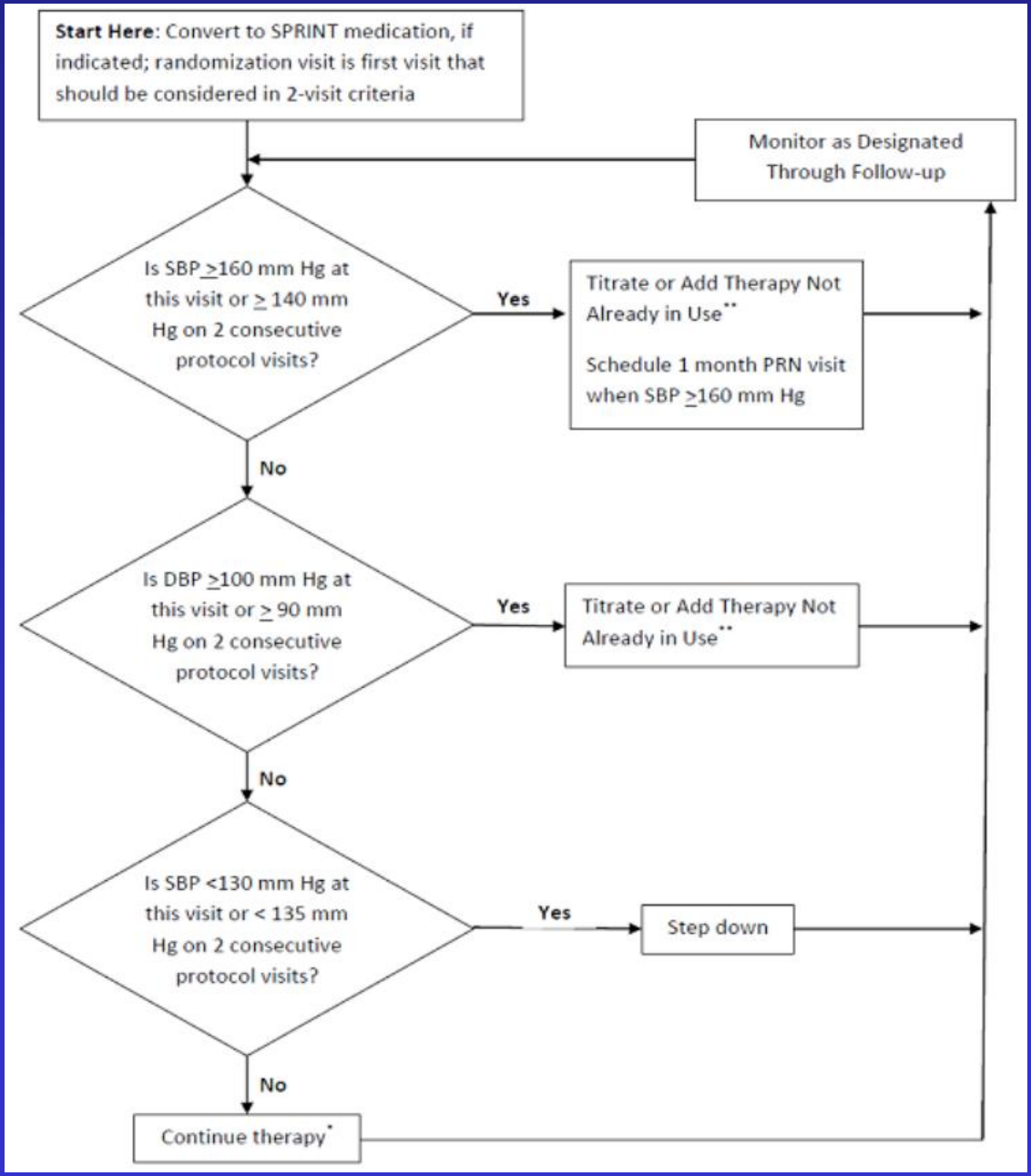
N Engl J Med 2015;373(22):2103-2116

SPRINT

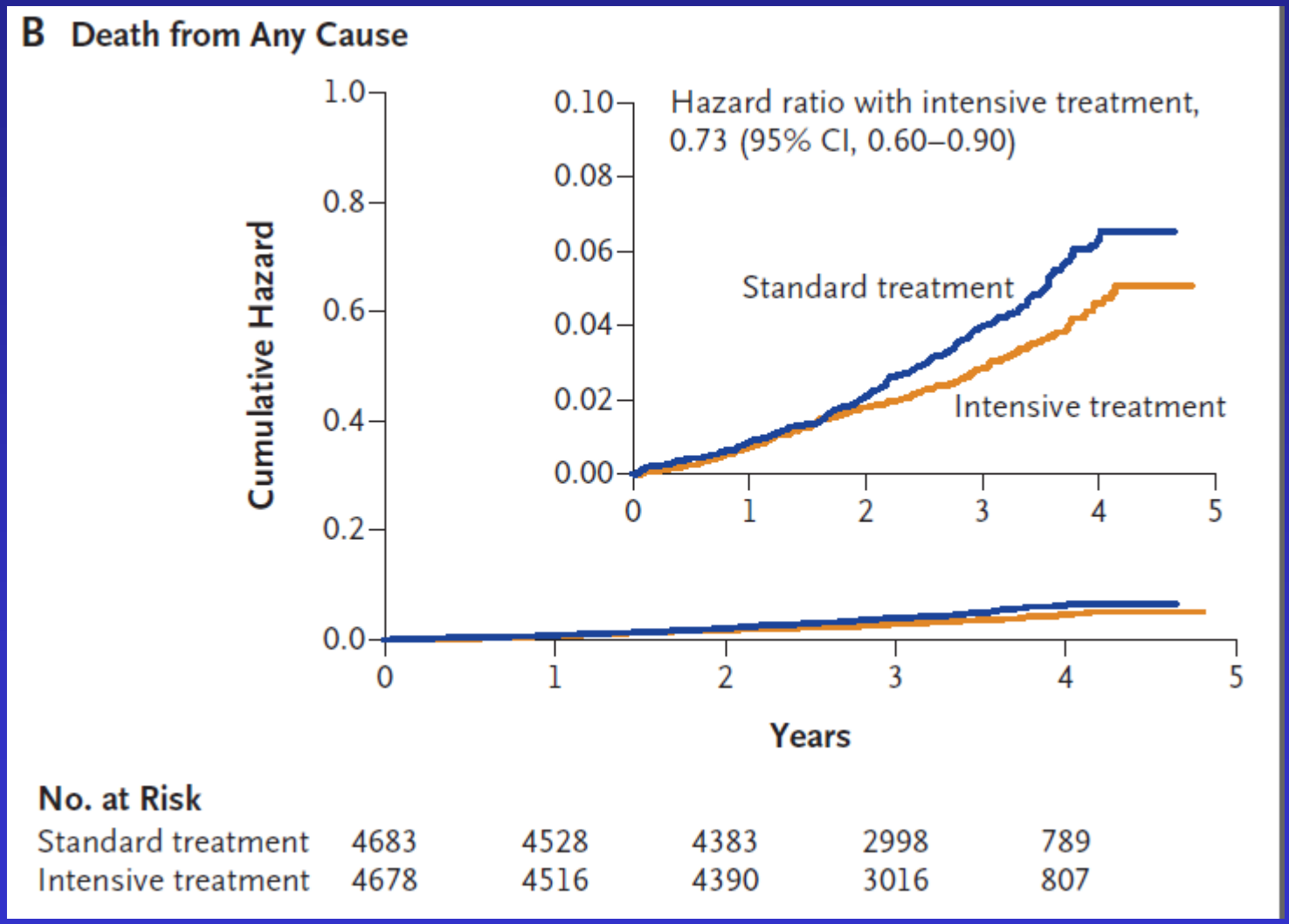
Intensive treatment arm



Standard treatment arm



SPRINT all cause mortality



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BP inclusion criteria

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
5. **Study final: 24.3% vs 6.9% on 4+ drugs.**

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