Treatment of Hypertension: What does the evidence say?

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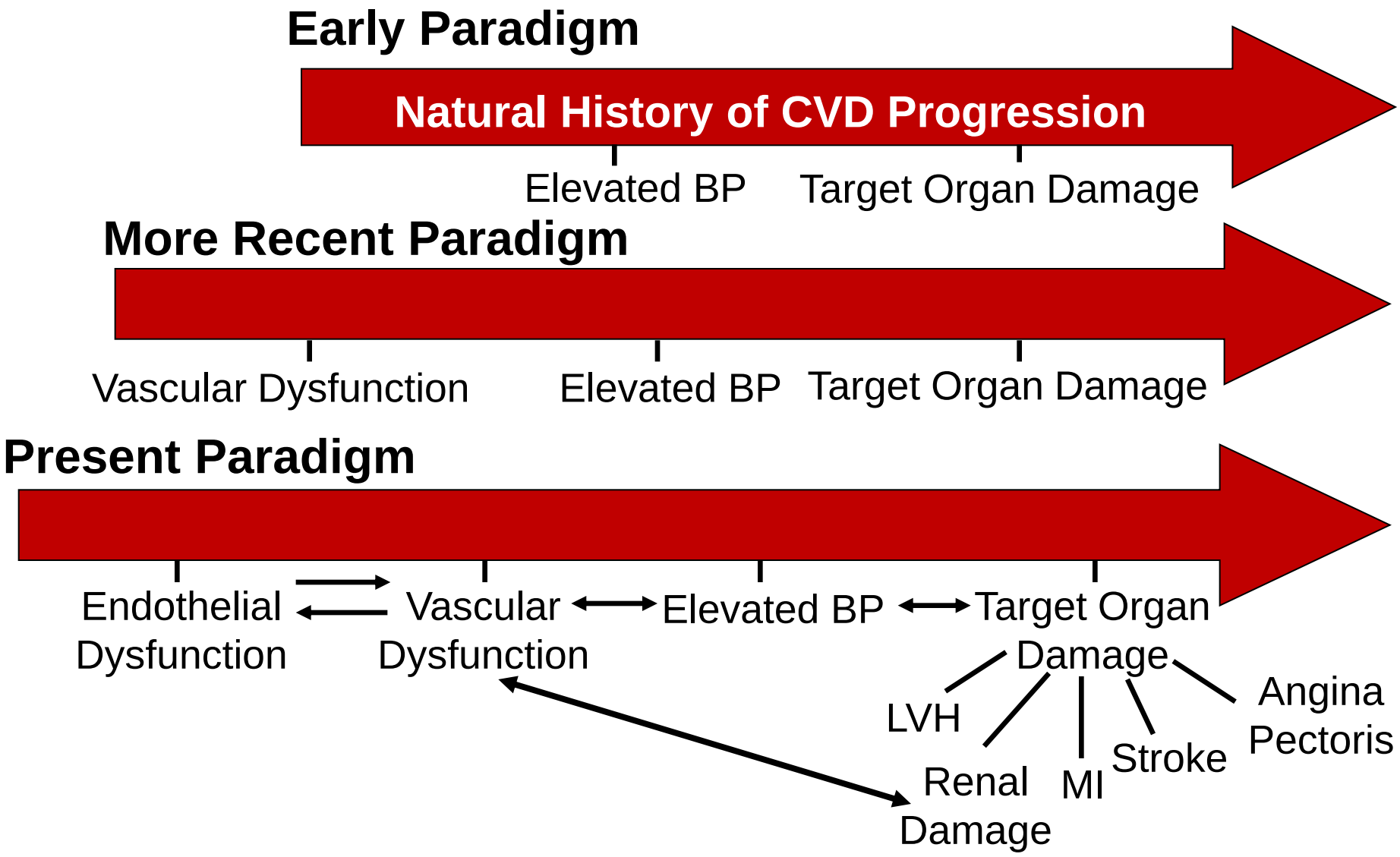
Question: What is the appropriate BP treatment threshold and target goal?

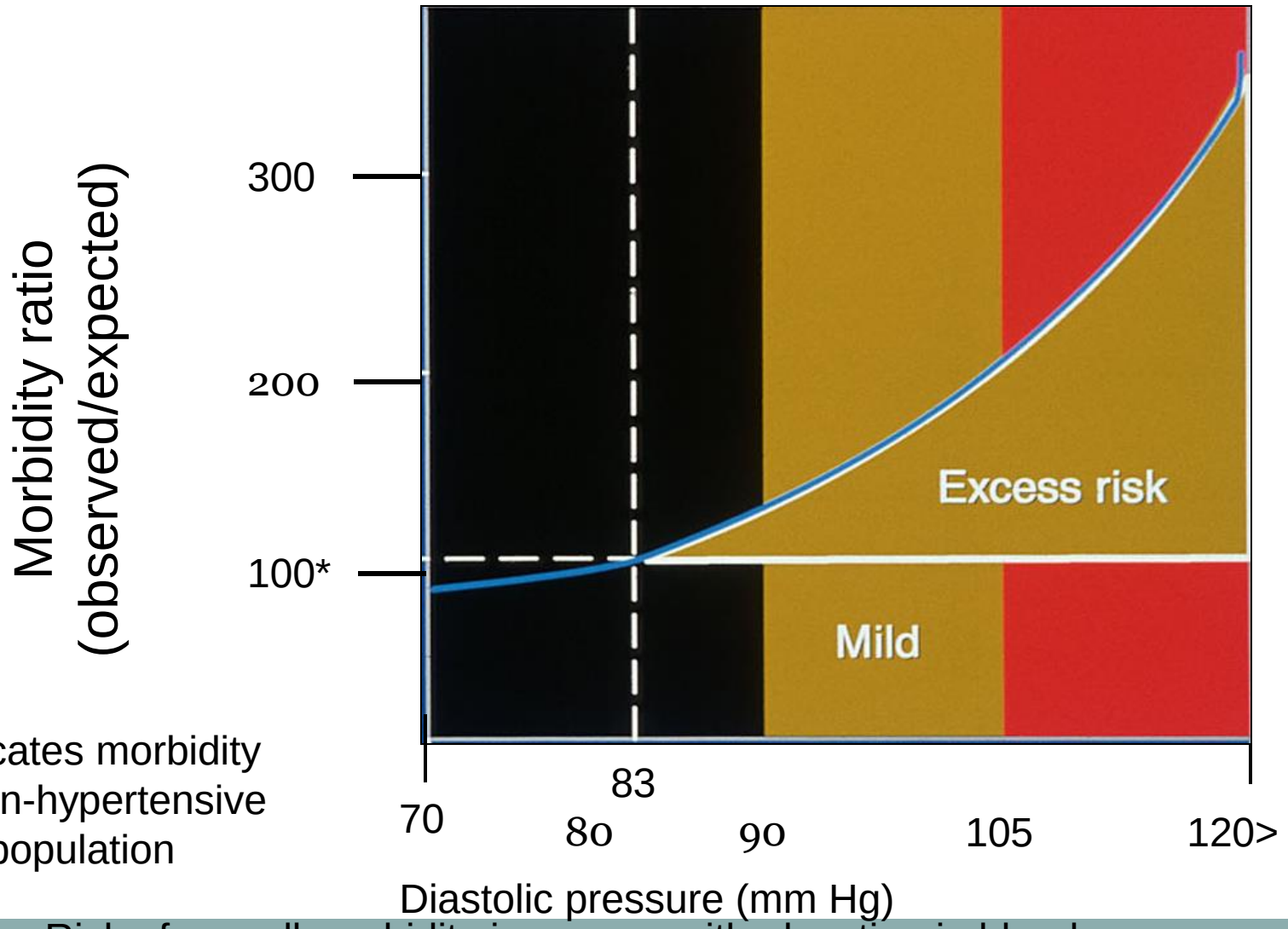
Consider two groups:

- The general population younger than 60 years of age.
- Those 60 years and older, at high cardiovascular risk, with diabetes, or chronic kidney disease.

Hypertension: The Disease Continuum



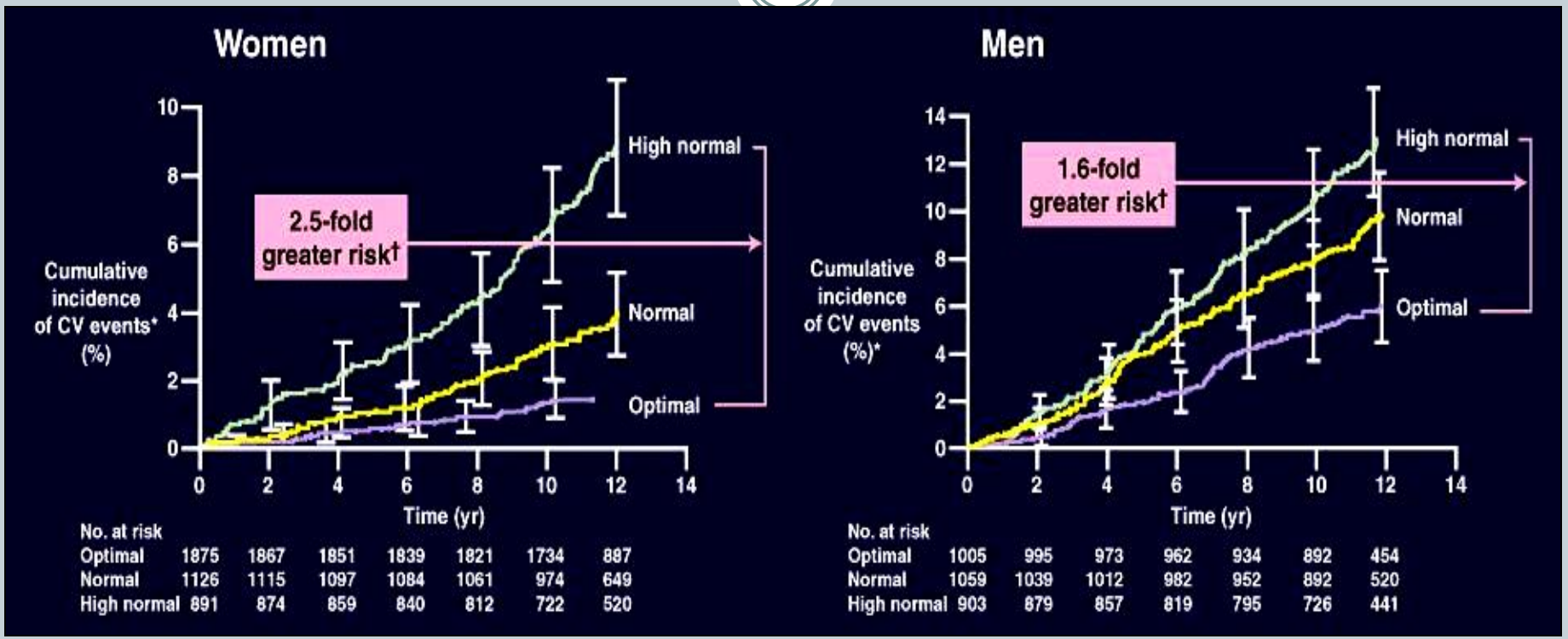
Relative Risk of Morbidity Compared to Non-Hypertensive Population



*Indicates morbidity for non-hypertensive population

Risk of overall morbidity increases with elevation in blood pressure

Framingham Heart Study
"High-normal" BP Is Not Benign



*CV death, MI, stroke, CHF
†Adjusted for concomitant CV risk factors
Optimal = <120/<80 mmHg
Normal = 120–129/80–84 mmHg
High normal = 130–139/84–89 mmHg

Vasan RS et al. *N Engl J Med.* 2001;345:1291–1297.

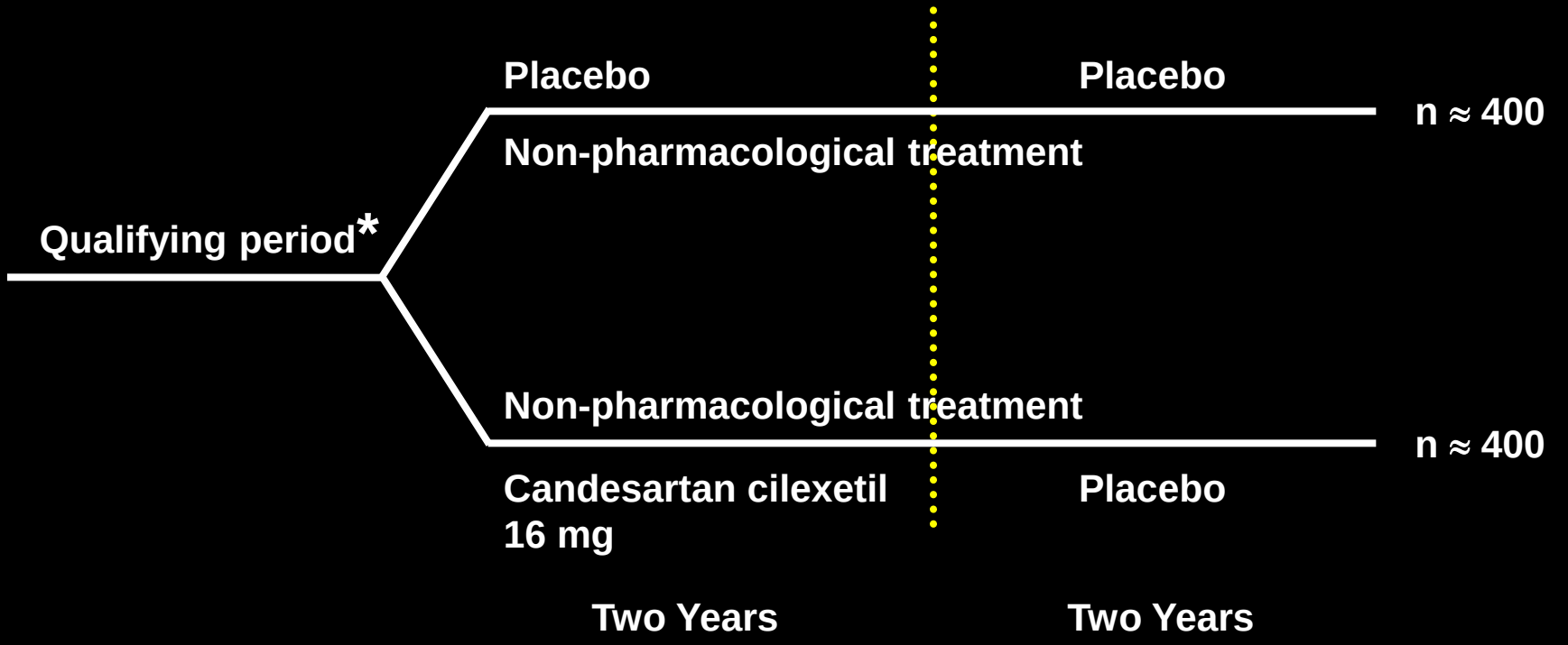
Treatment of Mild Hypertension Study (TOMHS): JAMA 1993

- 6 groups of patients (ages 45-69 years) with DBP <100 mmHg received nutritional-hygienic intervention (smoking, weight loss (nutrition advice), and exercise) and followed for 5 years and either:
- Placebo (n=234)
- Chlorthalidone (n=136)
- Acebutolol (n=132)
- Doxazosin (n=134)
- Amlodipine (n=131)
- Enalapril (n=135)

Treatment of Mild Hypertension Study: Results

- Baseline BP of all groups: 140/91 mmHg
- At 12 months: weight and urinary sodium decreased 4.5 kg and 23%, respectively and exercise increased 2-fold.
- SBP significantly less in drug treatment groups vs placebo group (-15.9 vs -9.1 mmHg; $p<0.001$)
- DBP significantly less in drug treatment groups vs placebo group (-12.3 vs -8.6 mmHg; $p<0.001$)
- No difference in either SBP or DBP reduction between the five drug treatment groups
- **Clinical events less with drug treatment vs. placebo group (-11.1% vs 16.2%; p=0.03)**

TROPHY – study design



*Clinic BP reading of 130-139/≤ 89 mm Hg or ≤ 139/85-89 mm Hg

Julius et al, Hypertension 2004

TROPHY: Risk of hypertension after two years with candesartan vs placebo, followed by two years of placebo vs placebo

Time point	Candesartan, n	Placebo, n	Relative risk (95% CI)	p
At two 2 years	53	154	66.3	<0.001
At four 4 years	208	240	15.6	<0.007

Julius S et al. *N Engl J Med* 2006;available at http://www.nejm.org

JNC-8 Committee: BP treatment threshold and target goal?

- In the general population, the treatment threshold is 140/90 mmHg and the target is <140/90 mmHg.
- Greater than 60 years of age, treatment threshold is 150/90 mmHg and the target is <150/90 mmHg.
- In individuals with diabetes and chronic kidney disease, the treatment threshold is 140/90 mmHg and the target is <140/90 mmHg

SPRINT Research Question

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

Randomized Controlled Trial
Target Systolic BP

Intensive Treatment	***Standard Treatment***
Goal SBP < 120 mm Hg	***Goal SBP < 140 mm Hg***

SPRINT design details available at:

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

SPRINT
Systolic Blood Pressure Intervention Trial

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

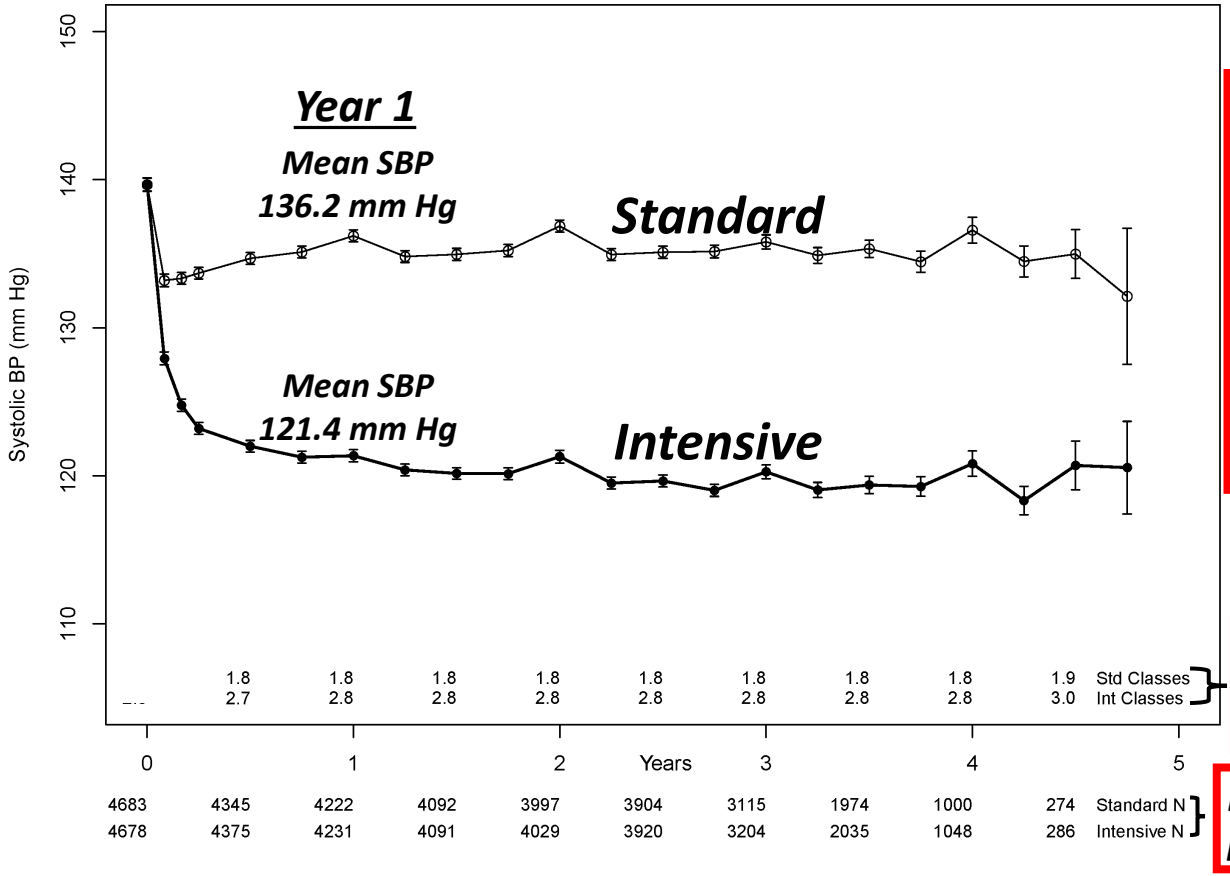
SPRINT
Systolic Blood Pressure Intervention Trial

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*

SPRINT
Systolic Blood Pressure Intervention Trial

Systolic BP During Follow-up



Average SBP

(During Follow-up)

Standard: 134.6 mm Hg

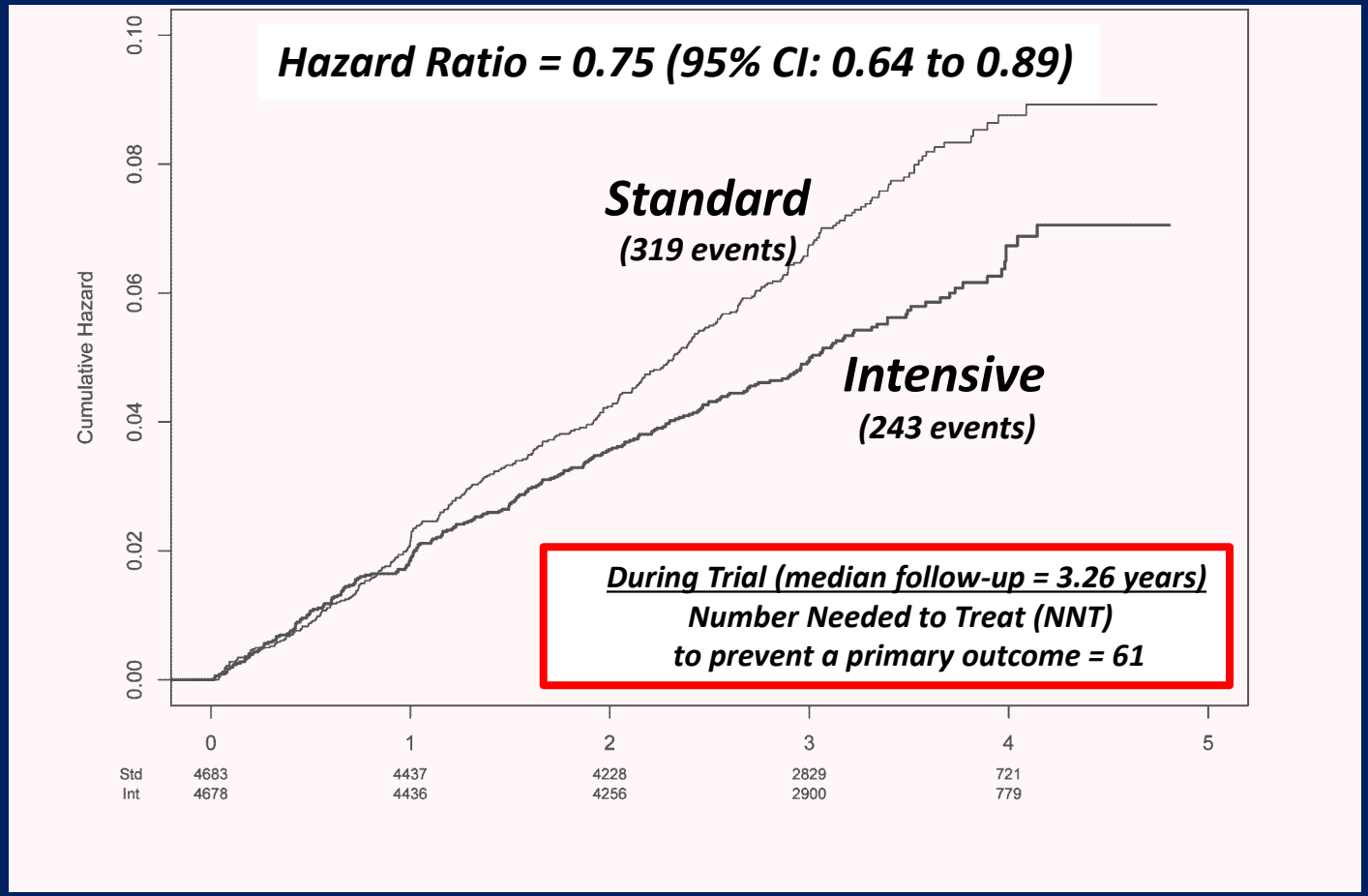
Intensive: 121.5 mm Hg

Average number of antihypertensive medications

Number of participants

SPRINT
Systolic Blood Pressure Intervention Trial

SPRINT Primary Outcome
Cumulative Hazard



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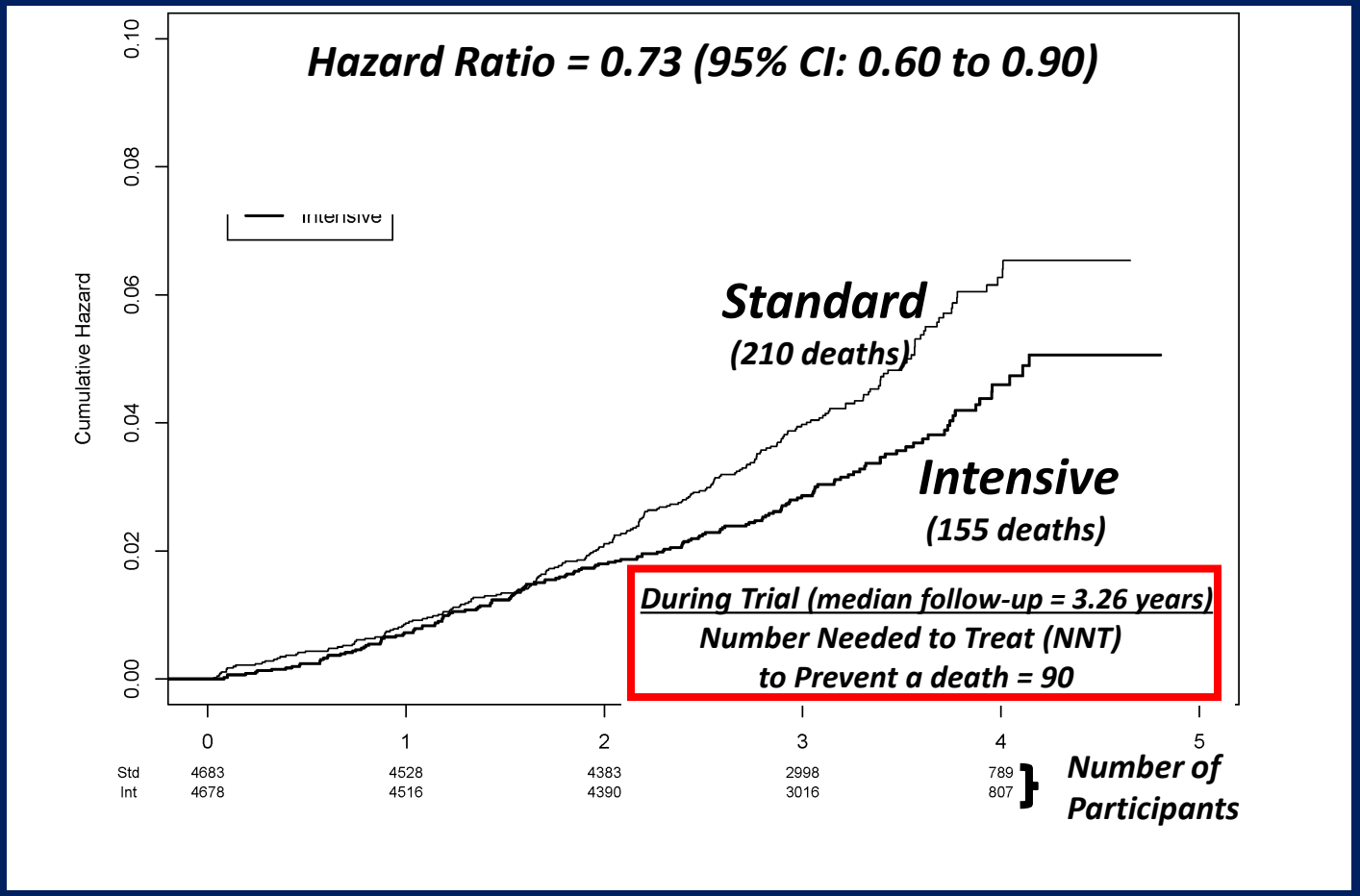
Systolic Blood Pressure Intervention Trial

All-cause Mortality
Cumulative Hazard



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Systolic Blood Pressure Intervention Trial

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

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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Systolic Blood Pressure Intervention Trial

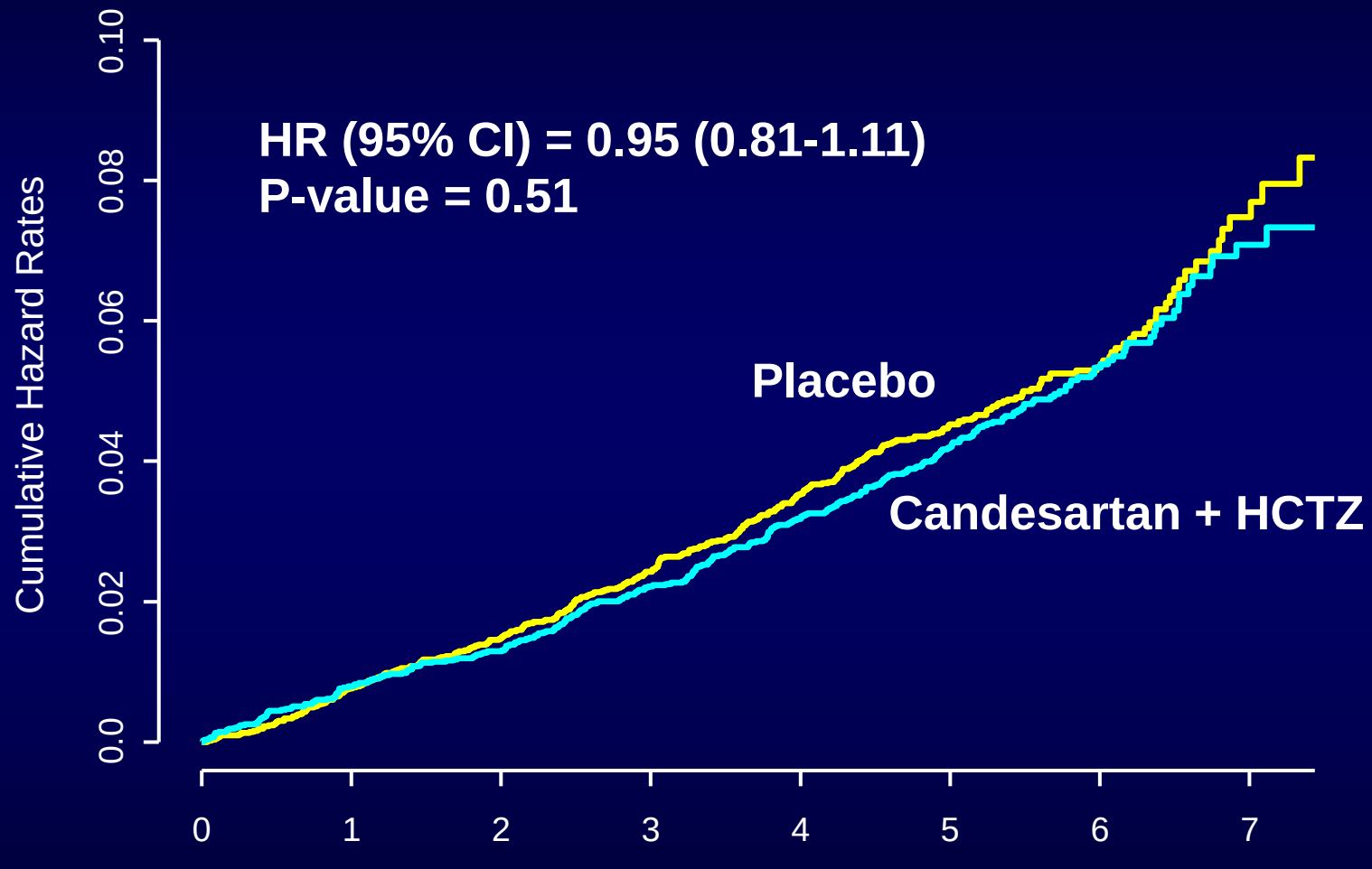
SPRINT: Clinically Important Caveats

- Intensive clinical research setting with close monitoring.
- Adherent, high cardiovascular risk patient population.
- Intensive BP group: more diuretics and RAAS inhibitors.
- Relative risk decreased only 0.5% with intensive BP reduction.
- BPs determined by an automated and non-observed approach in a quiet room after 5 minutes of rest which **COULD** result in a SBP as much as 10-12 mmHg **LOWER** than traditional BP measurements.
- Therefore, the SPRINT standard group SBP of 135 mmHg could be **145 mmHg** and the intensive group SBP of 122 mmHg could be **132 mmHg**.

Unique Aspects of HOPE-3

- BP lowering trial with wide range of BP entry criteria
- Cholesterol lowering treatment based on risk opposed to baseline LDL or HDL measurement
- Diverse population

CV Death, MI, Stroke, Cardiac Arrest, Revascularization, Heart Failure

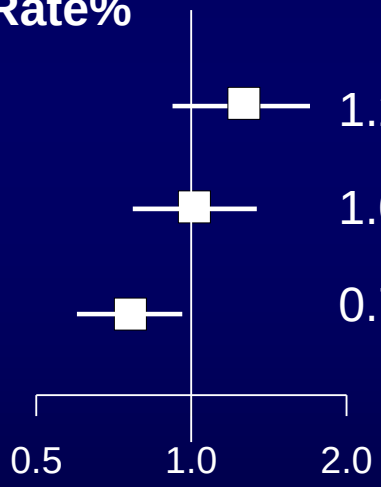


No. at Risk								
Cand + HCTZ	6356	6272	6200	6103	5968	4969	2076	522
Placebo	6349	6270	6198	6096	5967	4970	2075	488

Prespecified Subgroups: By Thirds of SBP

CV Death, MI, Stroke, Cardiac Arrest, Revasc, HF

Cutoffs	SBP Mean	Diff	Placebo Event Rate%	HR (95% CI)	P Trend
≤131.5	122	6.1	3.5	1.25 (0.92-1.70)	0.009
131.6-143.5	138	5.6	4.6	1.02 (0.77-1.34)	
>143.5	154	5.8	7.5	0.76 (0.60-0.96)	

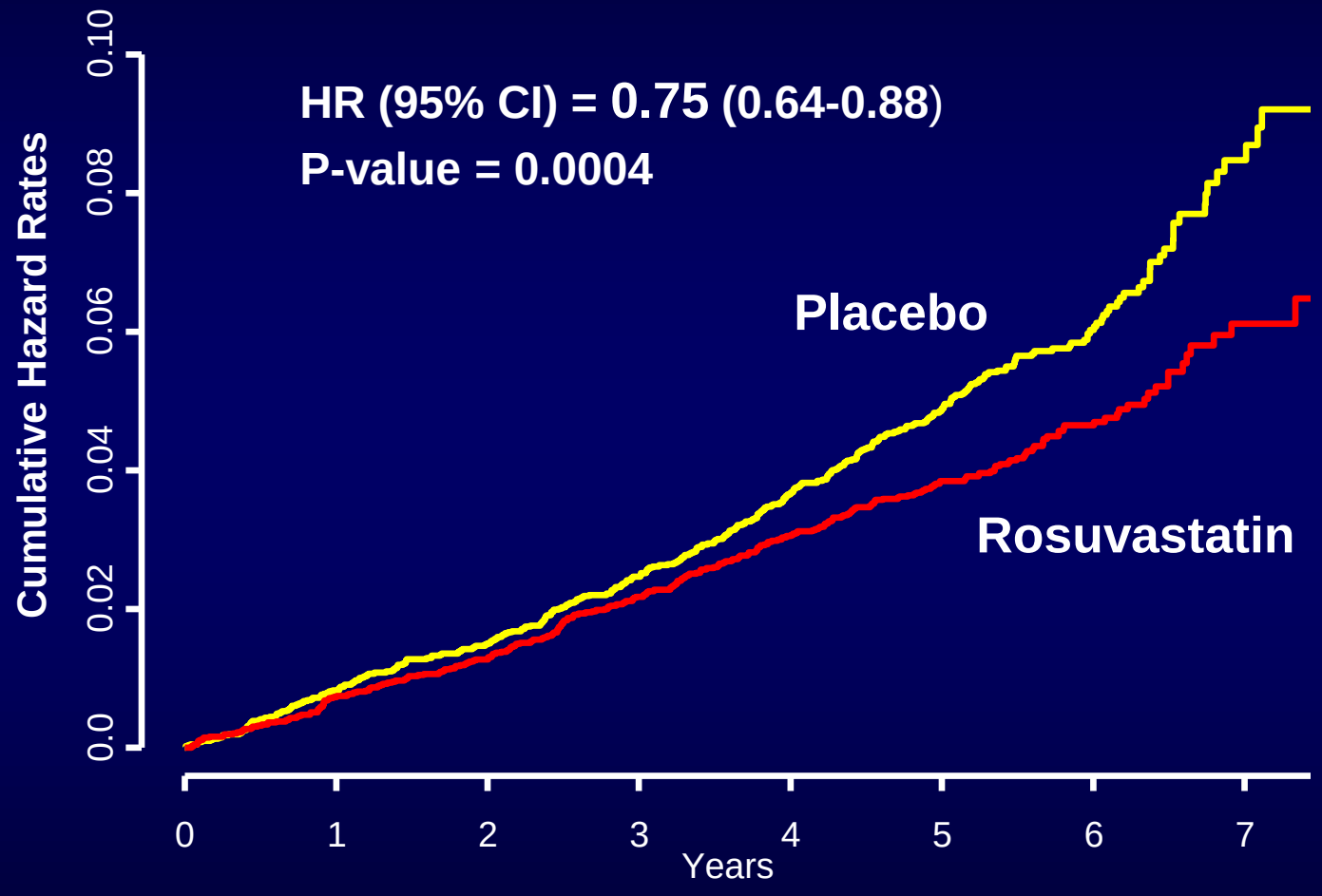


Candesartan + HCTZ Better Placebo Better

BP Lowering Arm: Conclusions

- Fixed dose combination of Candesartan 16 mg + HCTZ 12.5 mg/day reduced BP by 6.0/3.0 mmHg, but did not reduce CV events
- CV events were significantly reduced in the highest third of SBP
  - SBP >143.5 mmHg, mean 154 mmHg
- Results were neutral in the middle third, and trended towards harm in the lowest third of SBP
- Treatment increased lightheadedness, but not syncope or renal dysfunction

CV Death, MI, Stroke, Cardiac Arrest, Revasc, Heart Failure

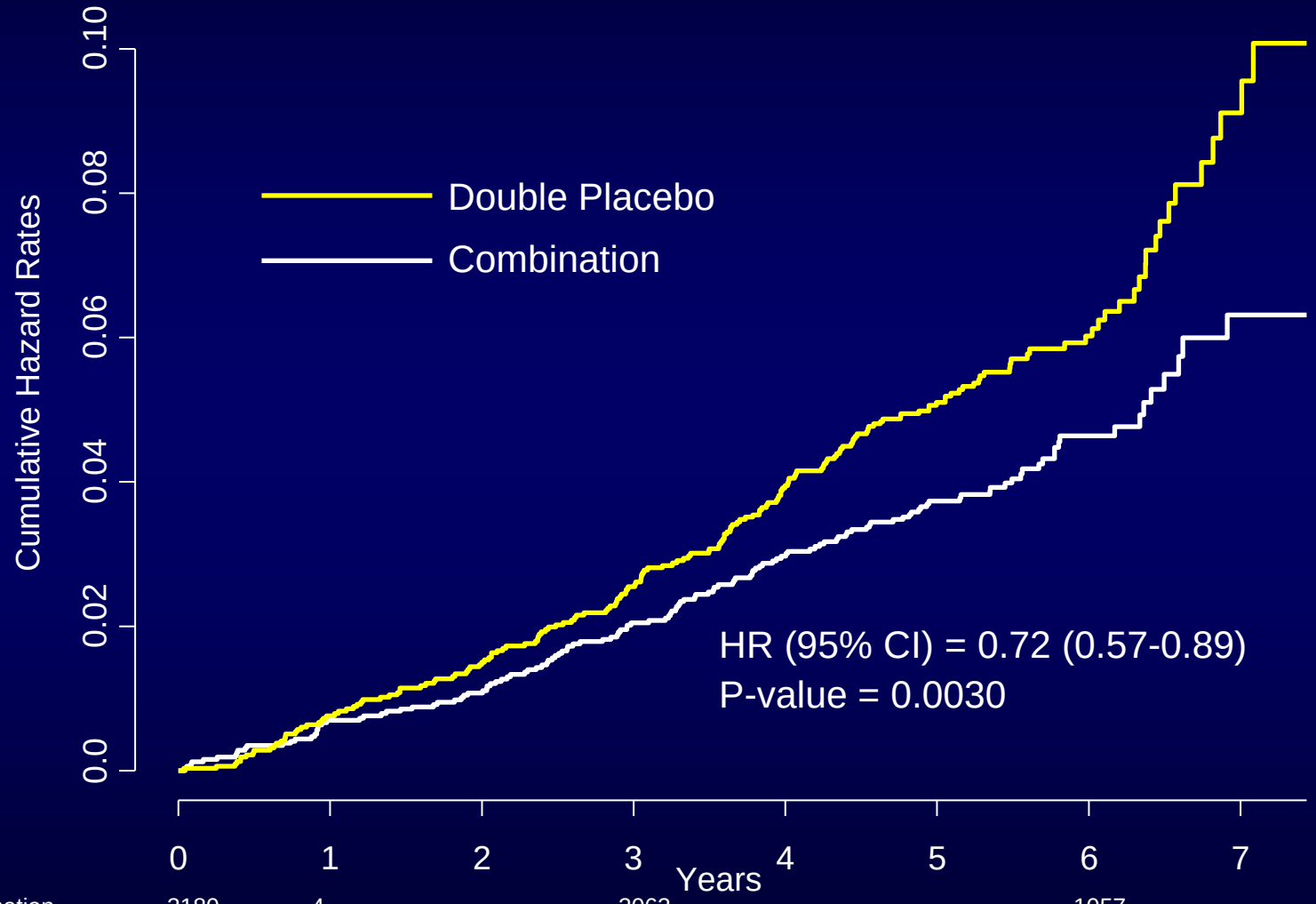


Rosuva	6361	6241	6039	2122
Placebo	6344	6192	5970	2073

Cholesterol Lowering: Conclusions

- Rosuvastatin 10mg/day reduced:
  - LDL-C by 34.6 mg/dl (0.9 mmol/l; i.e. 27% in LDL-C)
  - ***CVD by 25%***
- Consistent benefits regardless of:
  - LDL-C
  - SBP
  - Risk
  - CRP
  - Ethnicity
- Excess in muscle pain/weakness (reversible) and perhaps cataract surgery
- No excess in rhabdomyolysis, myopathy or new diabetes

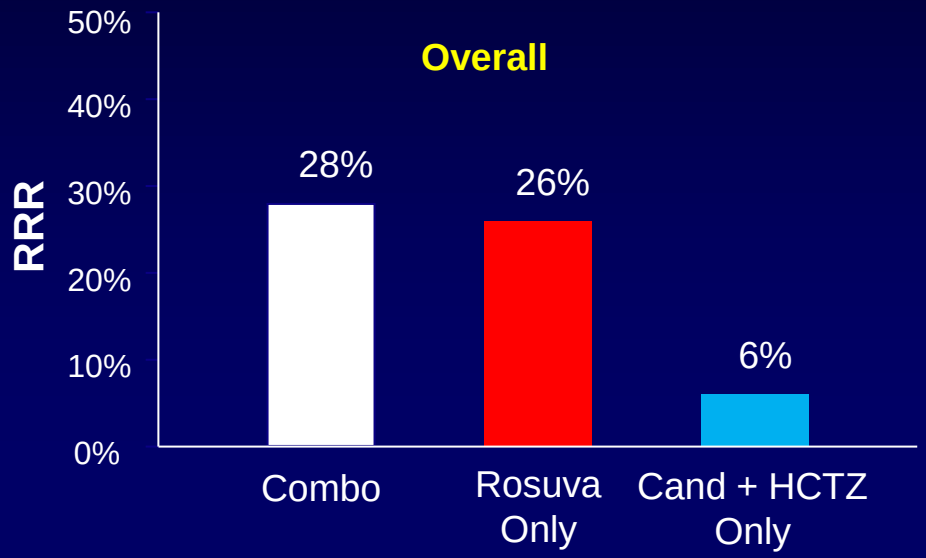
CV Death, MI, Stroke, Cardiac Arrest, Revasc, Heart Failure

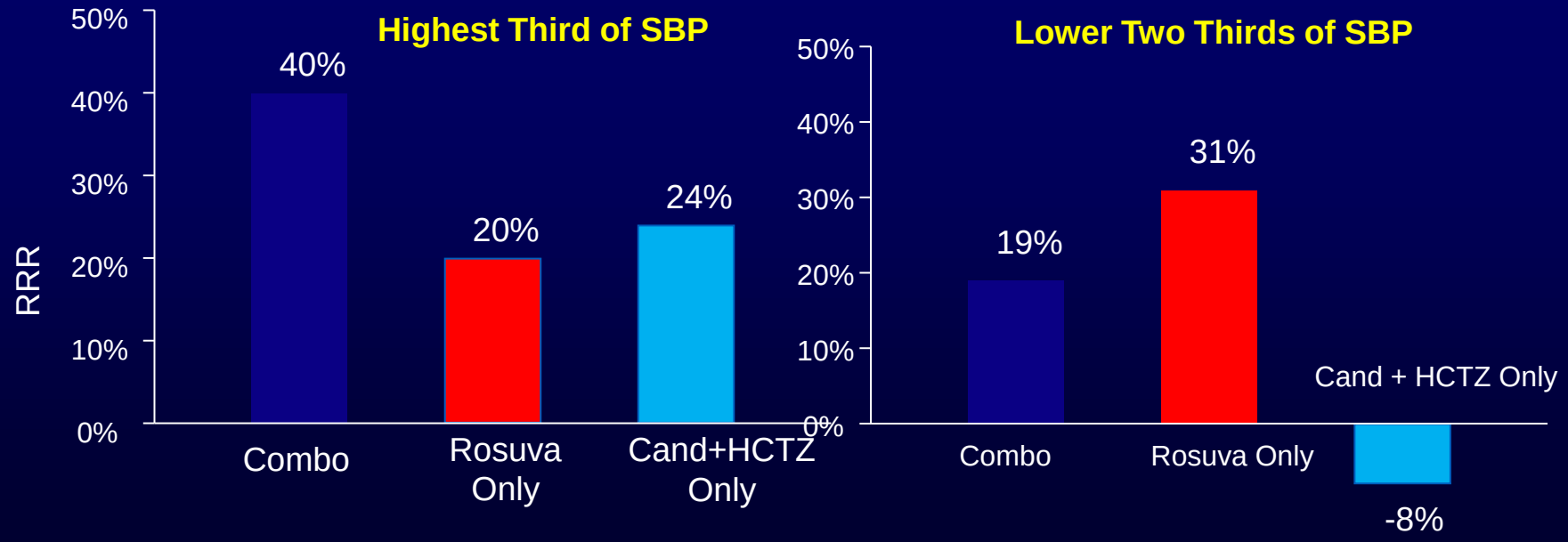


Combination	3180	4		3063			1057	
Rosuvastatin	3181			3061			1045	
Candesartan/HCTZ	3176			3040			1019	
Double Placebo	3168			3035			1030	

RRR of Combination and Each Intervention vs Double Placebo

Co-Primary 2





Clinical Implications

- Statins beneficial in ***intermediate-risk*** individuals without CVD
- BP lowering benefits only those with elevated BP
- Combined BP & cholesterol lowering:
  - Leads to a 40% risk reduction in hypertensives (benefits from *both* BP lowering and statin)
- In others, 30% RRR from statin alone
- Pragmatic strategy:
  - No Lipid or BP entry criteria or targets
  - No Dose titration
  - Infrequent safety monitoring

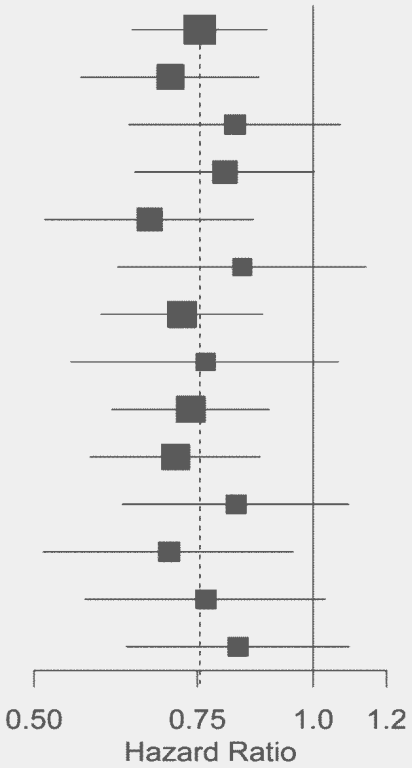
Strategy used in HOPE-3 is simple, safe and effective and widely applicable

PATIENTS WITH HYPERTENSION 60 YEARS OF AGE OR GREATER

SPRINT Primary Outcome Experience in the Six Pre-specified Subgroups of Interest: Age 75 years and greater

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)	

*Unadjusted for multiplicity
*Treatment by subgroup interaction



SPRINT
Systolic Blood Pressure Intervention Trial

Age 60 years and older: BP treatment threshold and target goal

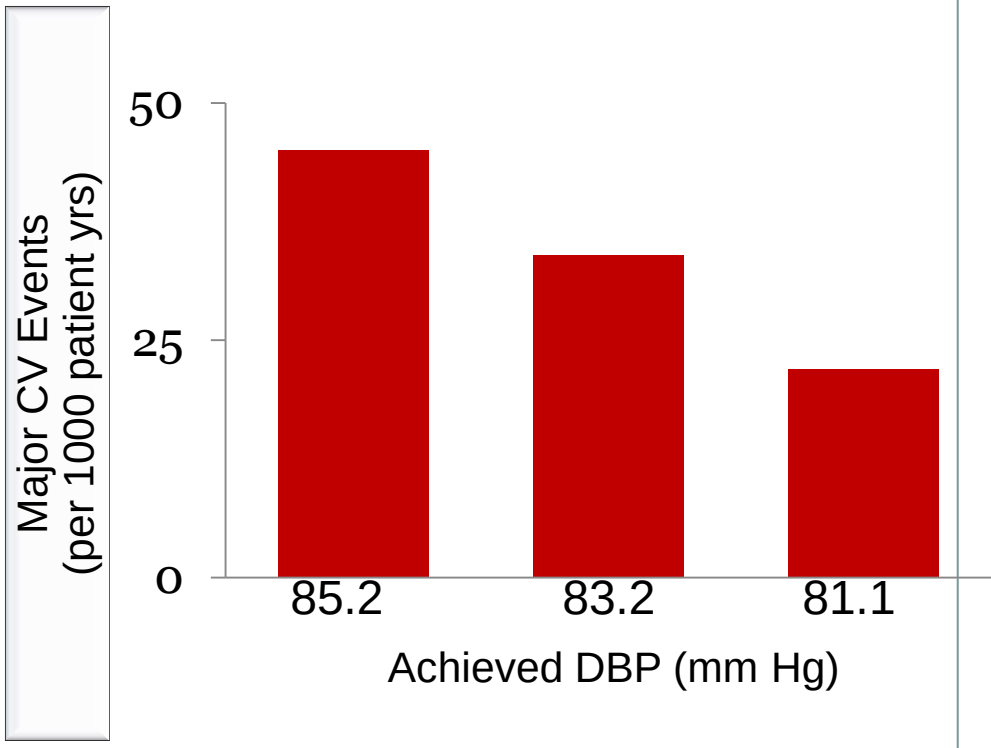
- JNC-8: Treatment threshold 150/90 mmHg and target goal <150/90 mmHg.
- AHA, ASH-ISH, ESC-ESH: Treatment threshold 140/90 mmHg and target goal <140/90 mmHg.
- ACP-AAFP (2017 and post SPRINT): Follows JNC-8. However, if history of stroke, TIA, or high CV risk, may treat to <140/90 mmHg.

PATIENTS WITH HYPERTENSION AND DIABETES

Benefits of BP Reduction in HOT: Diabetic Cohort

Target DBP (mm Hg)	Achieved SBP (mm Hg)	Achieved DBP (mm Hg)
≤90	143.7	85.2
≤85	141.4	83.2
≤80	139.7	81.1

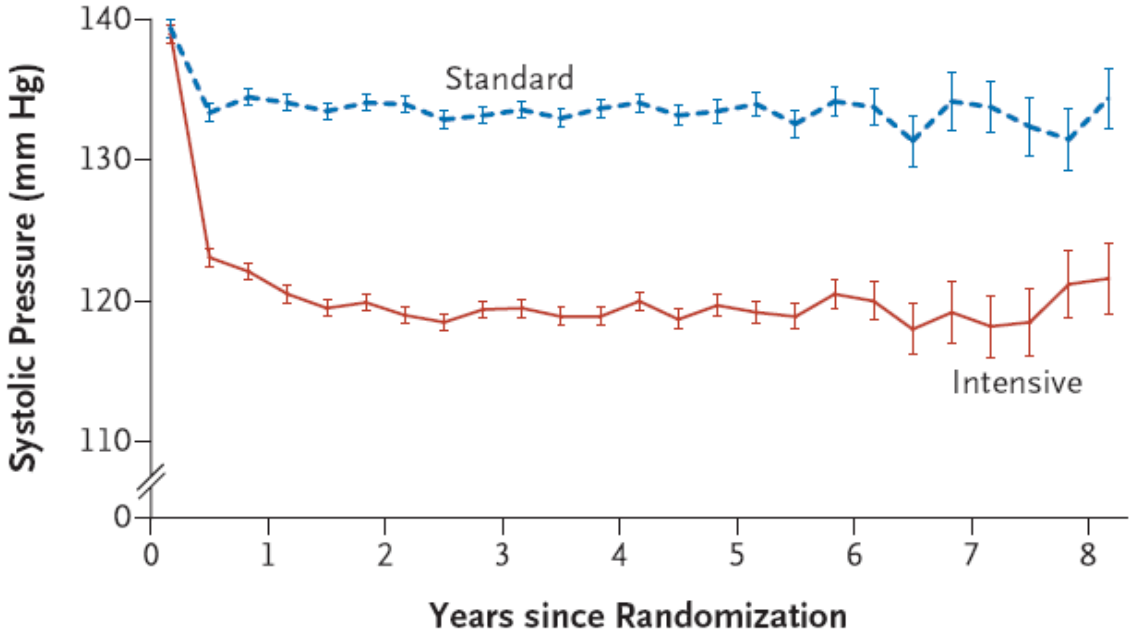
Achieved = mean of all BPs from 6 months of follow-up to end of study



P = 0.05 for trend

Hansson L et al. *Lancet. 1998;351:1755-1762*.

ACCORD STUDY: Intensive Blood Pressure Control in Type 2 Dm



Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

Figure 1. Mean Systolic Blood-Pressure Levels at Each Study Visit.

I bars indicate 95% confidence intervals.

NEJM 2010; 362 (17); 1575

ACCORD STUDY: Intensive Blood Pressure Control in Type 2 Dm

Table 3. Primary and Secondary Outcomes.

Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74
Primary outcome plus revascularization or nonfatal heart failure	521	5.10	551	5.31	0.95 (0.84–1.07)	0.40
Major coronary disease event†	253	2.31	270	2.41	0.94 (0.79–1.12)	0.50
Fatal or nonfatal heart failure	83	0.73	90	0.78	0.94 (0.70–1.26)	0.67

* The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

† Major coronary disease events, as defined in the protocol, included fatal coronary events, nonfatal myocardial infarction, and unstable angina.

NEJM 2010; 362 (17); 1575

ACCORDIAN (2015): Follow-up to ACCORD

- ACCORD ended in 2009. About 4000 patients were still followed (87% of the total patients still alive).
- Main result: Significant interaction between BP and glycemic control.
- In patients with standard BS control, intensive BP reduction decreased CV events (21%, $p<0.08$)

Hypertension and Diabetes: BP treatment threshold and target goal

- JNC-8: Treatment threshold of 140/90 mmHg and target goal <140/90 mmHg.

- American Diabetes Association (2017):

Same as JNC-8, except may treat to <130/80 mmHg in high CV risk individuals.

If 160/100 mmHg, initiate two drug therapy.

SPRINT Primary Outcome Experience in the Six Pre-specified Subgroups of Interest: Chronic Kidney Disease

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
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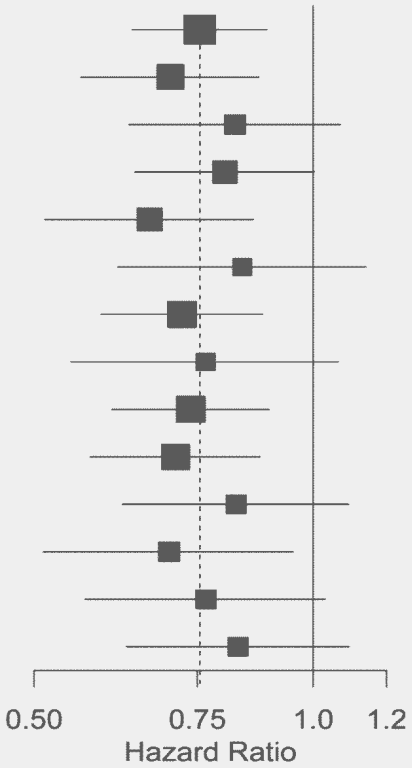

SPRINT
Systolic Blood Pressure Intervention Trial

Patients with Chronic Kidney Disease: BP treatment threshold and target goal

- JNC-8: Treatment threshold 140/90 mmHg and target goal <140/90 mmHg.
- In SPRINT patients with CKD appeared to benefit less from intensive BP reduction and appeared to have a greater incidence of side effects especially acute kidney injury.
- Full publication on SPRINT-CKD coming shortly.

CONCLUSIONS: Where are we going in 2017?

- ACC-AHA guidelines should be out later this year.
- Is Pre-hypertension the new Hypertension? If so drug treatment for all? Only those at high CV risk with a target of <130/80.
- General Population: Threshold 140/90 mmHg and target 130/80 mmHg or less including those with diabetes and chronic kidney disease.
- Recent ACC-AHA guidelines: Reduced and preserved CHF: BP goal <130/80 mmHg

Thank You