Implications of SPRINT and Intensive BP Management: Should it be Expanded to Diabetes?

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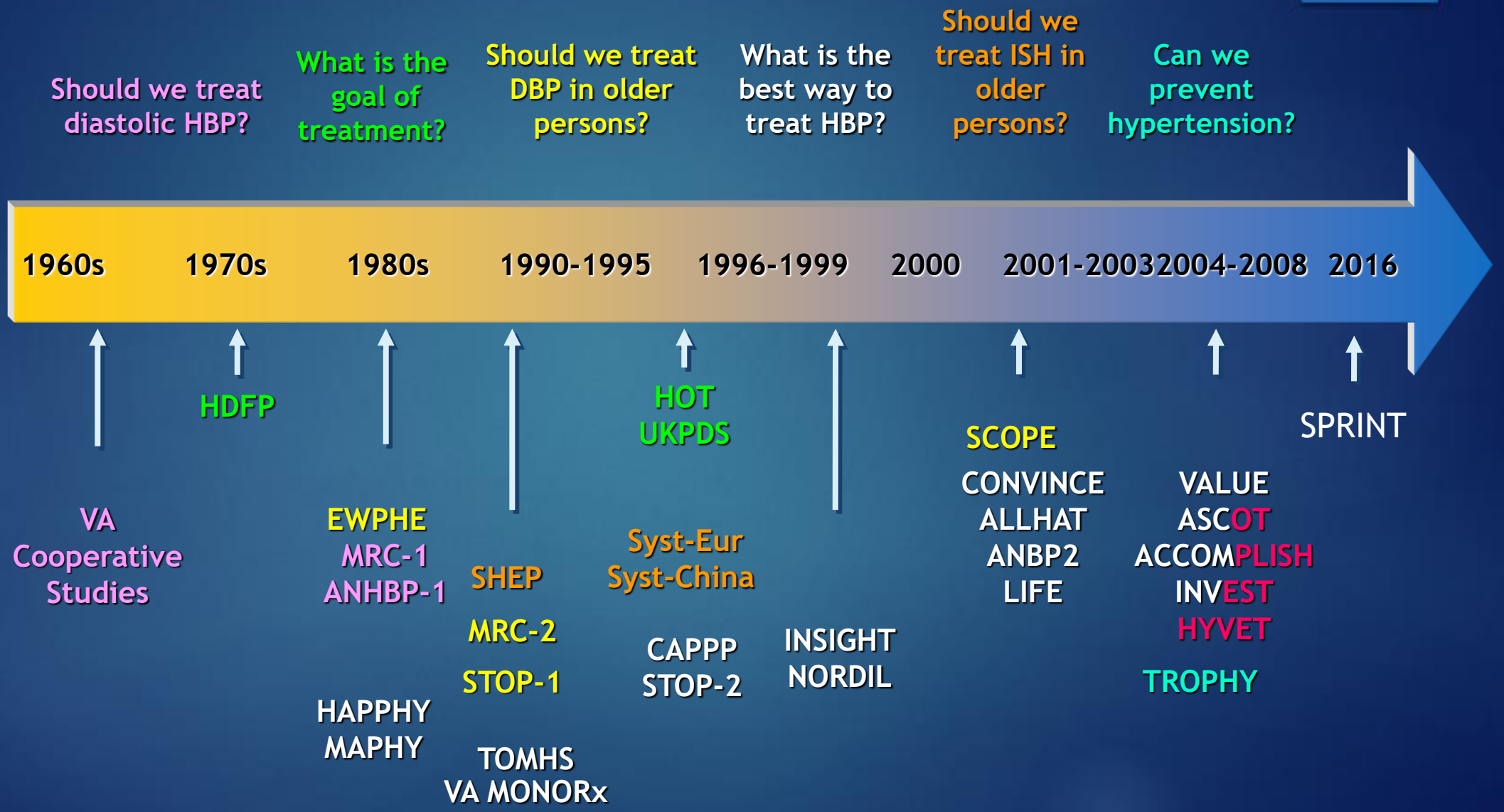
Clinical Trials in Hypertension



Peixoto AJ and **Bakris GL**. IN Kimmel P and Rosenberg ME (Eds.) Chronic Renal Disease Elsevier, Academic Press, New York, 2015-pp.455-469.

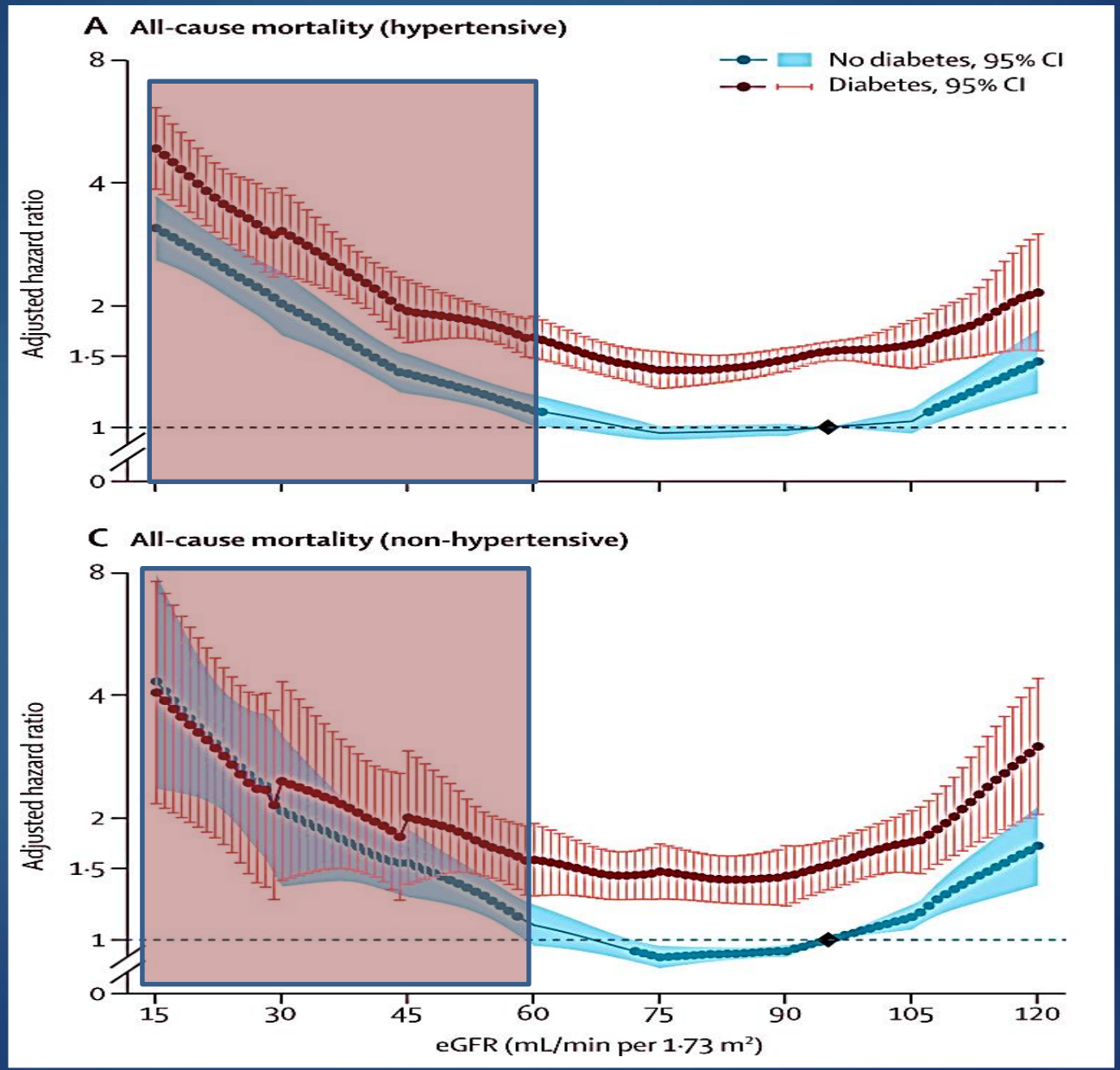
What is the Goal BP and Initial Therapy in Kidney Disease or Diabetes to Reduce CV Risk?

Group	Goal BP (mmHg)	Initial Therapy
ADA (2016)	<140/90	ACE Inhibitor/ARB*
Expert Panel +KDIGO/KDOQI (NKF) (2013)	<140/90	ACE Inhibitor/ARB
ESH (2007+ 2009)	<130/80	ACE Inhibitor/ARB*
KDOQI (NKF) (2004)	<130/80	ACE Inhibitor/ARB*
JNC 7 (2003)	<130/80	ACE Inhibitor/ARB*
Am. Diabetes Assoc (2003)	<130/80	ACE Inhibitor/ARB*
Canadian HTN Soc. (2002)	<130/80	ACE Inhibitor/ARB*
Am. Diabetes Assoc (2002)	<130/80	ACE Inhibitor/ARB*
Natl. Kidney Foundation (2000)	<130/80	ACE Inhibitor*
British HTN Soc. (1999)	<140/80	ACE Inhibitor
WHO/ISH (1999)	<130/85	ACE Inhibitor
JNC VI (1997)	<130/85	ACE Inhibitor

*** Indicates use with diuretic**

Categories	NICE* 2011	ESH/ESC 2013	ASH / ISH 2014	AHA/ACC/CDC 2013	JNC 8* 2014
Definition of hypertension	**≥140/90 and daytime ABPM (or home BP) ≥135/85**	**≥140/90**	**≥140/90**	**≥140/90**	Not addressed
Drug therapy/ low-risk patients after non-pharm treatment	≥160/100 or day-time ABPM ≥ 150/95	≥140/90	≥140/90	≥140/90	< 60 y. ≥140/90 ≥ 60 y. ≥150/90
β-blockers – first-line drug	**No**	Yes	**No**	**No**	**No**
Diuretic	Chlorthalidone - indapamide	thiazides chlorthalidone, indapamide	thiazides chlorthalidone, indapamide	thiazides	thiazides chlorthalidone, indapamide
Initial single pill combo Rx	Not mentioned	markedly elevated BP	**≥160/100**	**≥160/100**	**≥160/100**
BP targets	**< 140/90 ≥ 80 y. < 150/90**	**<140/90 ; < 80, SBP 140-150 SBP <140 in fit patients Elderly ≥ 80 y. SBP 140-150**	**<140/90 ≥ 80 y. < 150/90**	**<140/90 Lower targets may be appropriate in some patients, including the elderly**	**< 60 y. <140/90 ≥ 60 y. <150/90**
BP target in diabetes	Not addressed	**< 140/85**	**<140/90**	**<140/90 -Consider Lower targets**	**<140 /90**

Associations of CKD with Mortality and End-stage Renal Disease in Individuals With and Without Diabetes: a Meta-analysis



Fox et.al. Lancet 2012;380:1662-1673.

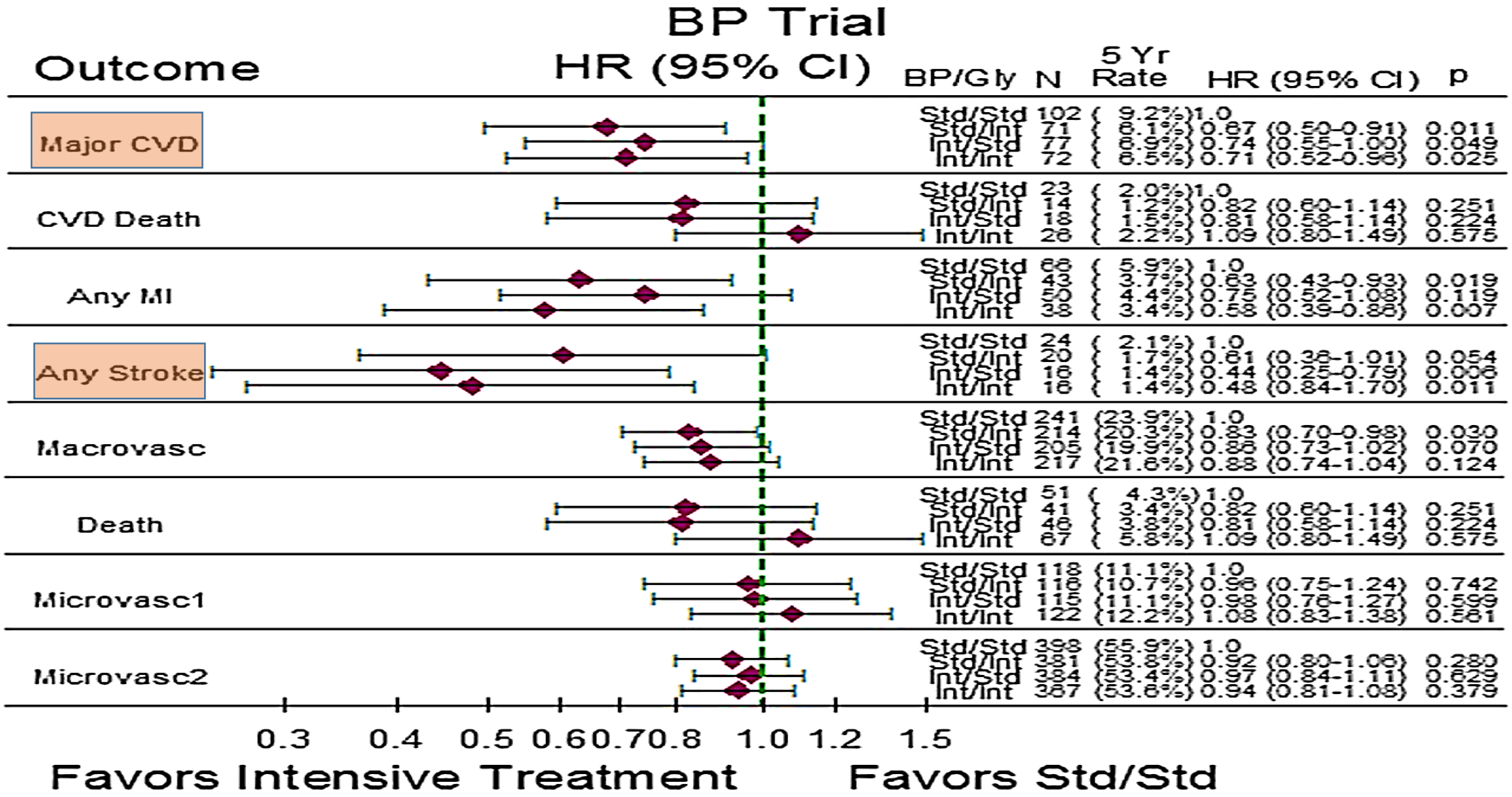
ACCORD BP Study: Primary and Secondary Outcomes

- Patients with T2D and hypertension (N = 4733)
- Random assignment
  - Intensive therapy: target SBP < 120 mm Hg
  - Standard therapy: target SBP < 140 mm Hg
- 1° outcome: nonfatal MI, nonfatal stroke, death from CV causes
- Mean follow-up = 4.7 y

Outcome	Intensive	Standard	HR	*P*-value
SBP after 1 year (mmHg)	119.3	133.5	NR	NR
1° outcome (annual rate)	1.87	2.09	0.88	.20
Death from any cause (annual rate)	1.28	1.19	1.07	.55
Stroke (annual rate)	0.32	0.53	0.59	.01
AEs (rate)	3.3	1.3	NR	<.001

Cushman et.al. N.Engl.J.Med. 2010;362 :1575-1585.

Five-year Event Rates Comparing the Three More Intensively Treated Groups to the Standard BP-lowering/Standard Glucose-lowering Treatment Groups ACCORD.



Margolis et al. Diabetes Care 2014;37:1721-1728

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

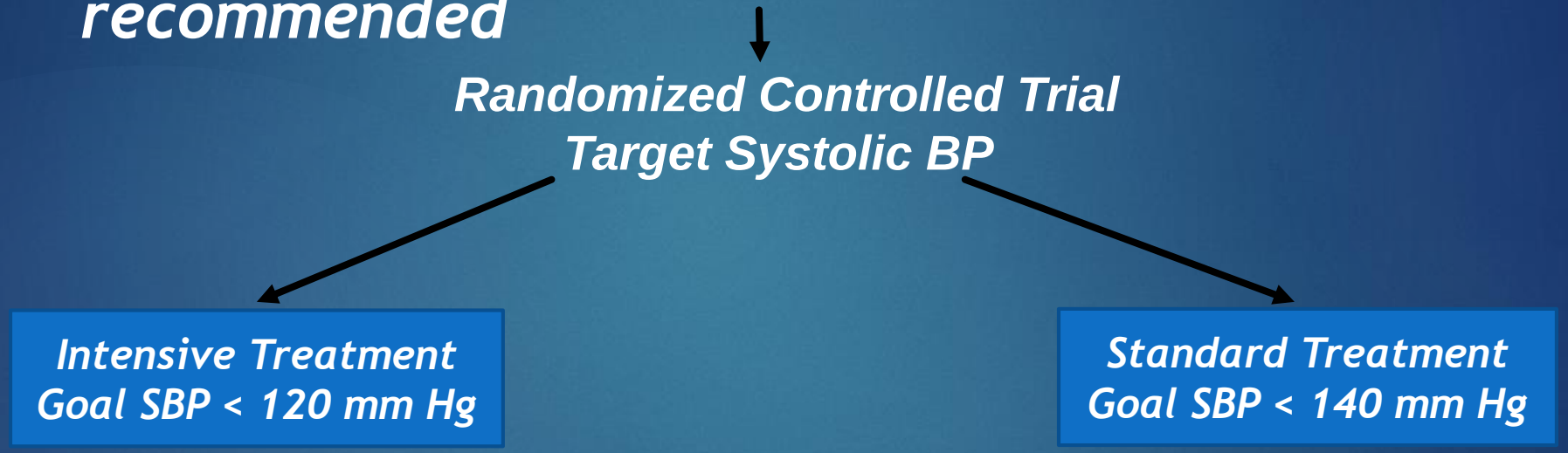
A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

SPRINT Research Question

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



SPRINT design details available at:

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

Methods

- Open-label RCT sponsored by NHLBI at 102 sites in the USA
- An independent data and safety monitoring board
- **INCLUSION CRITERIA**: Age >50, Systolic BP 130-180 mmHg, and increased CV risk
  - **Increased CV risk defined as ≥1 of the following:**
    - **Clinical or subclinical CV disease other than CVA**
    - **CKD (eGFR < 60)**
    - **10-year ASCVD risk ≥15% based on Framingham**
    - **Age >75**

Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

Methods cont'd

- **EXCLUSION CRITERIA**:
  - DM
  - Prior CVA
  - eGFR <20 or ESRD
  - ACS or revascularization within past 3 months
  - One-minute standing BP < 110 mmHg
  - LVEF <35% OR symptomatic HF within past 3 months
  - Other standard exclusions (poor prognosis from other disease, transplant patients, pregnancy, non-compliance, substance abuse, etc.)

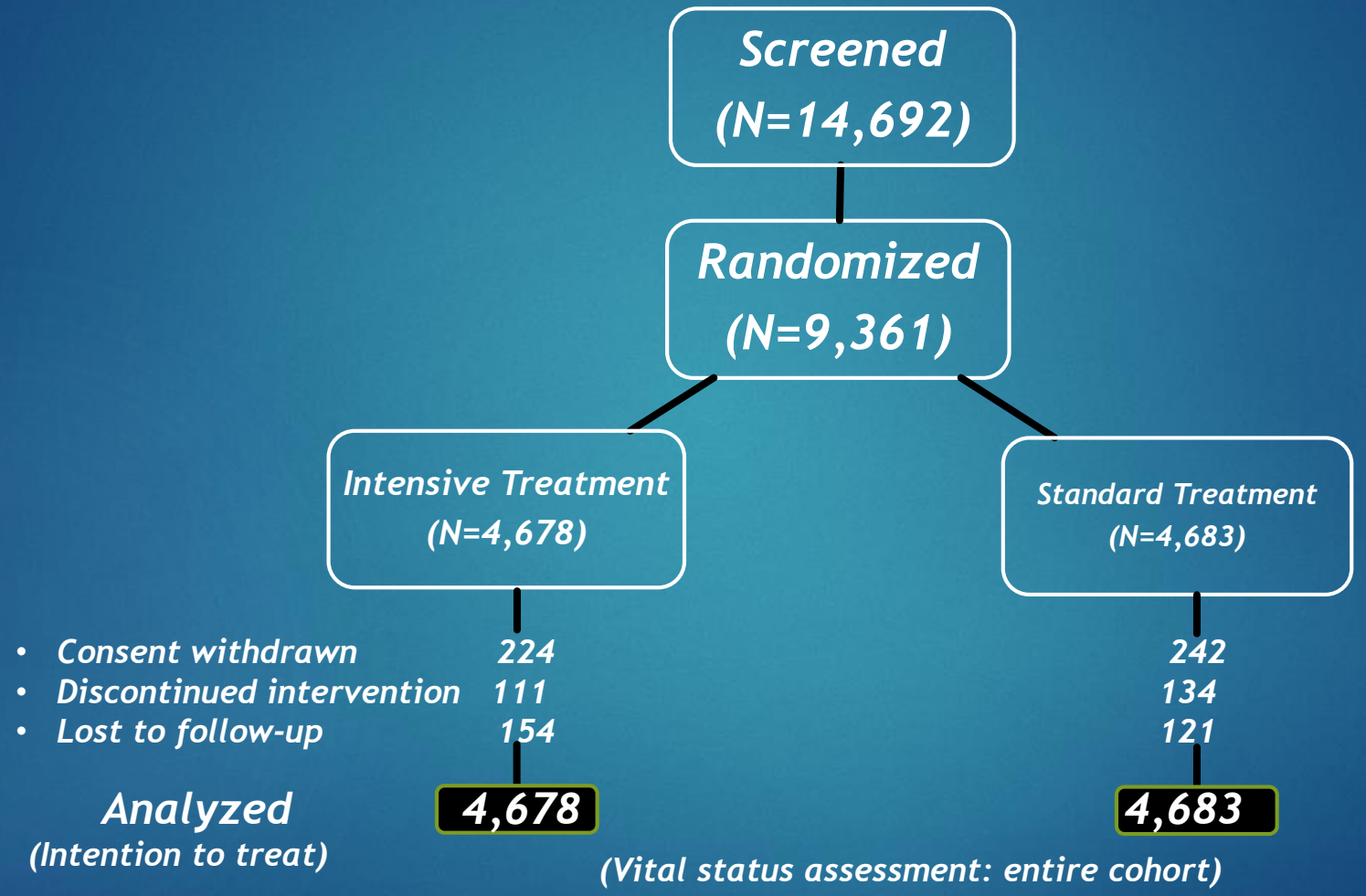
Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

Methods cont'd

- Participants and study personnel were aware of group assignments, but outcome adjudicators were not
- Treatment algorithms & formulary were similar to ACCORD
- All medications provided for free
- Investigators could also prescribe any other antihypertensive meds as needed
- Investigators were encouraged to use the most evidence-based drug classes and drugs within each class (i.e., chlorthalidone vs HCTZ, amlodipine vs other CCB, loops in advanced CKD patients, BB in CAD patients, etc.)

Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

SPRINT: Enrollment and Follow-up Experience



Wright et.al. N.Engl.J.Med. 2015;373 : 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)	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)

Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

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)

Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

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)*

Wright et.al. N.Engl.J.Med. 2015;373 : 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.

Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

Additional Prespecified 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*

Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

Blood Pressure Intervention

- Participants seen monthly for first 3 months, and then every 3 months thereafter
- Meds adjusted monthly based on BP - 3 separate values averaged at each office visit, and taken after patient was seated quietly for 5 minutes.
- All measurements made with same automated BP cuff machine across sites – Omron Model 907
- Target <120 mmHg in intensive group
- Target 135-139 mmHg in standard group
  - Dose(s) were reduced in standard group if BP <130 mmHg or <135 mmHg on 2 consecutive visits

Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

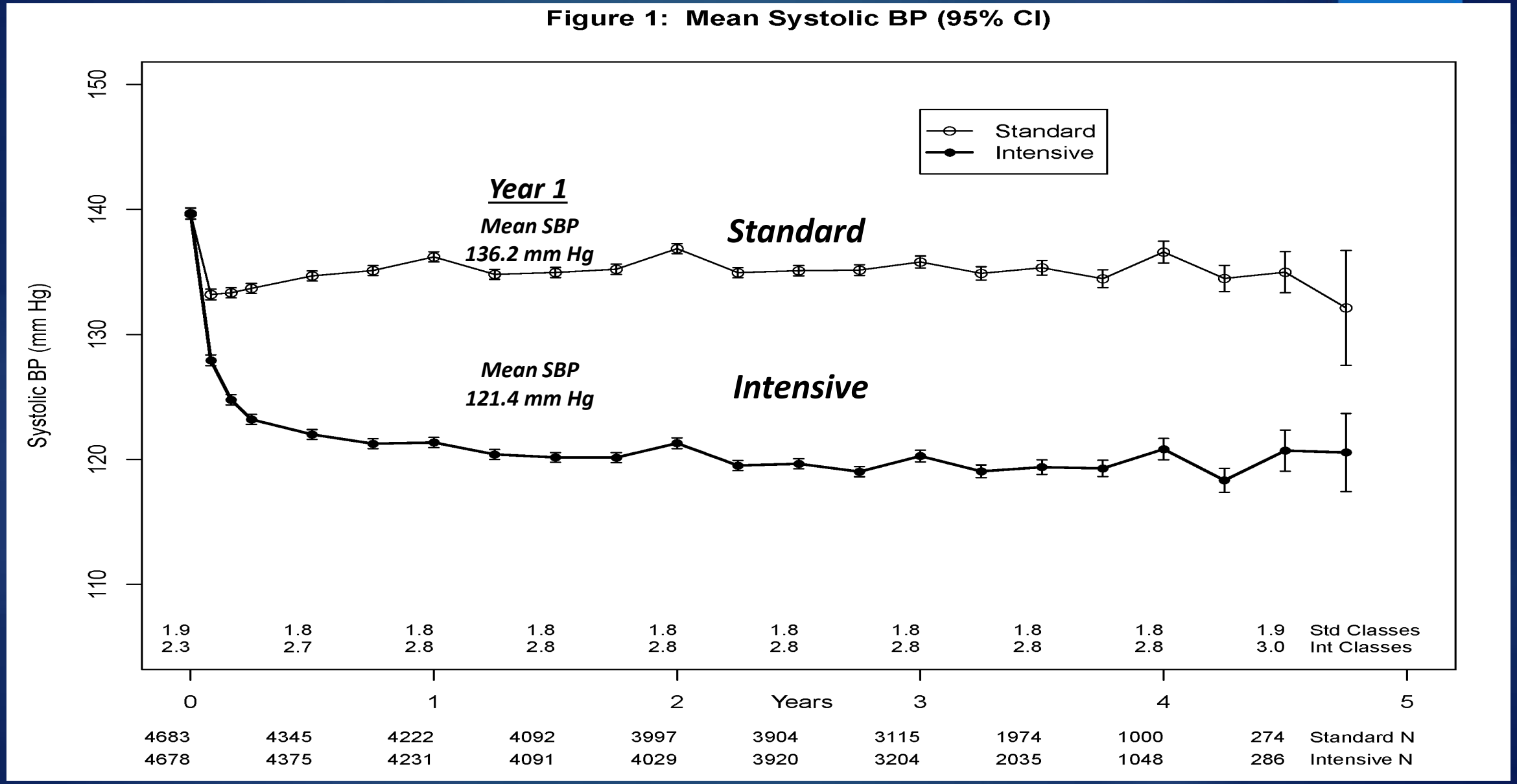
Medication Used

Table S2. Utilization of Antihypertensive Medication Classes at Most Recent Visit

	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)**

Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

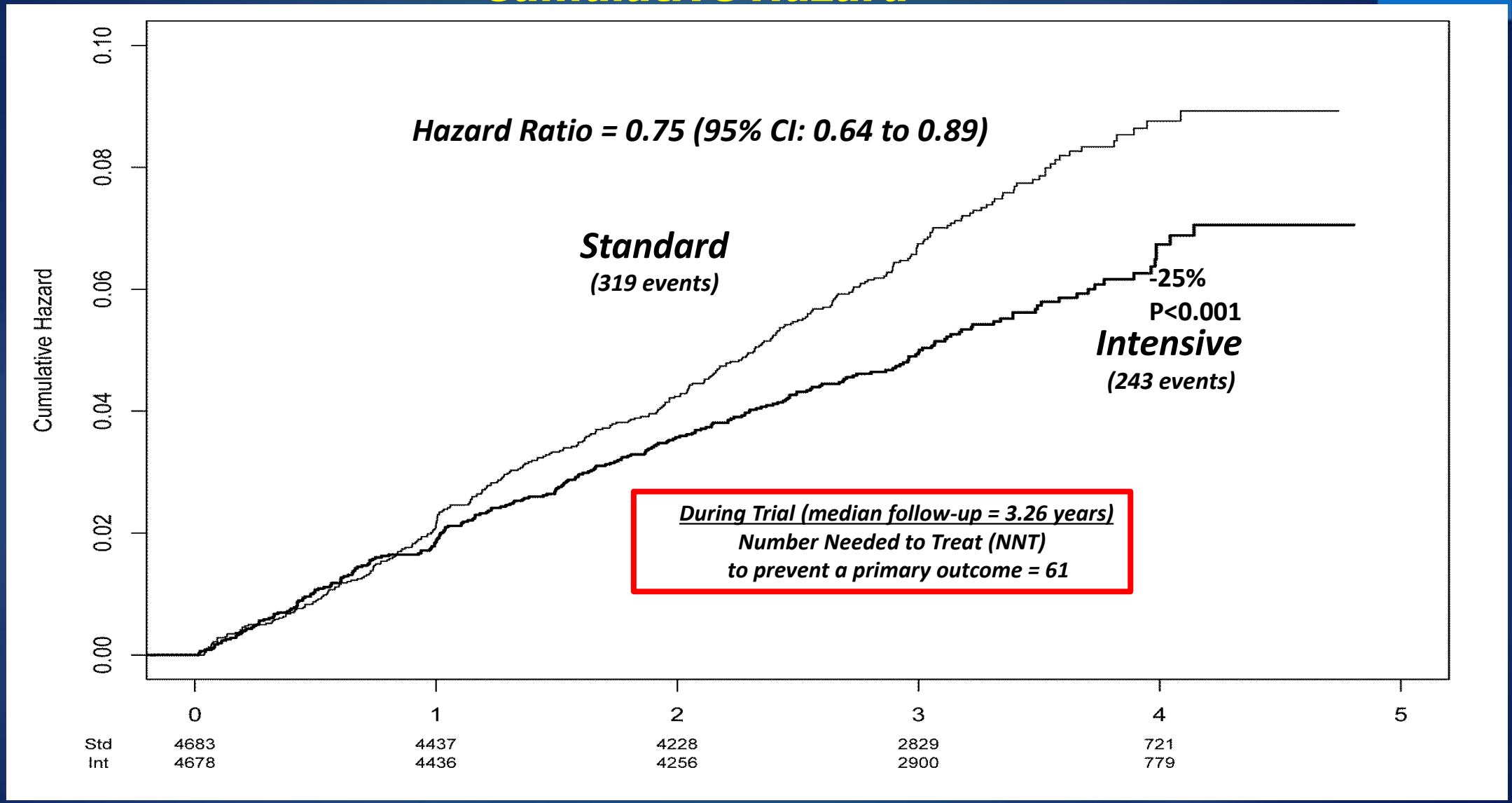
Blood Pressure Change During Follow up



Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

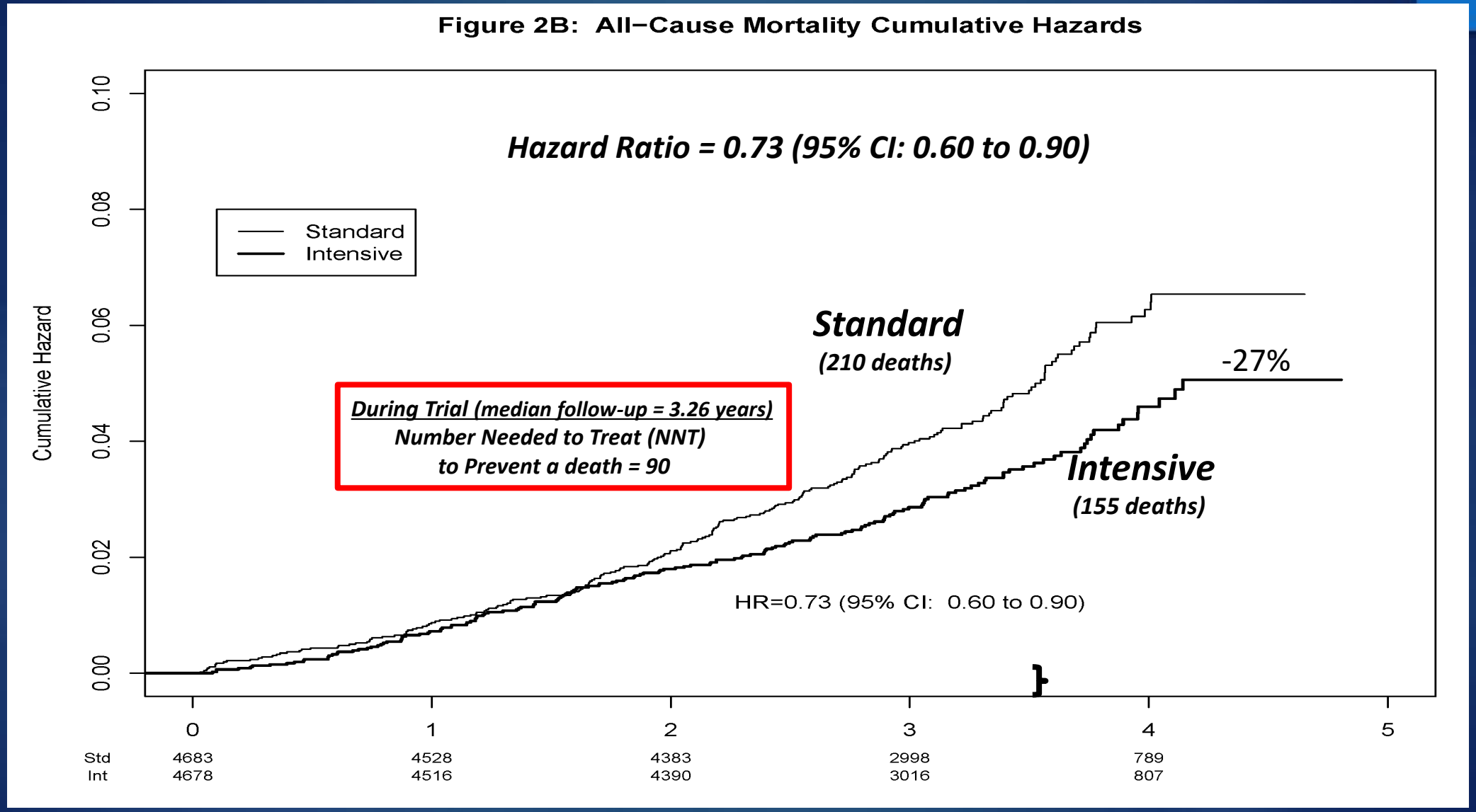
SPRINT Primary Outcome

Cumulative Hazard



Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

All-cause Mortality



Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

Primary and Secondary Outcomes and Renal Outcomes

Table 2. Primary and Secondary Outcomes and Renal Outcomes.*

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% per year*	*no. of patients (%)*	*% per year*		
All participants	**(N=4678)**		**(N=4683)**			
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001
Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002
Death from cardiovascular causes	37 (0.8)	0.25	65 (1.4)	0.43	0.57 (0.38–0.85)	0.005
Death from any cause	155 (3.3)	1.03	210 (4.5)	1.40	0.73 (0.60–0.90)	0.003
Primary outcome or death	332 (7.1)	2.25	423 (9.0)	2.90	0.78 (0.67–0.90)	<0.001
Participants with CKD at baseline	**(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 in estimated GFR§	10 (0.8)	0.23	11 (0.8)	0.26	0.87 (0.36–2.07)	0.75
Long-term dialysis	6 (0.5)	0.14	10 (0.8)	0.24	0.57 (0.19–1.54)	0.27
Kidney transplantation	0		0			
Incident albuminuria¶	49/526 (9.3)	3.02	59/500 (11.8)	3.90	0.72 (0.48–1.07)	0.11
Participants without CKD at baseline‖	**(N=3332)**		**(N=3345)**			
≥30% reduction in estimated GFR to <60 ml/min/1.73 m^2§	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

Wright et.al.
N.Engl.J.Med.
2015;373 : 2103-2116

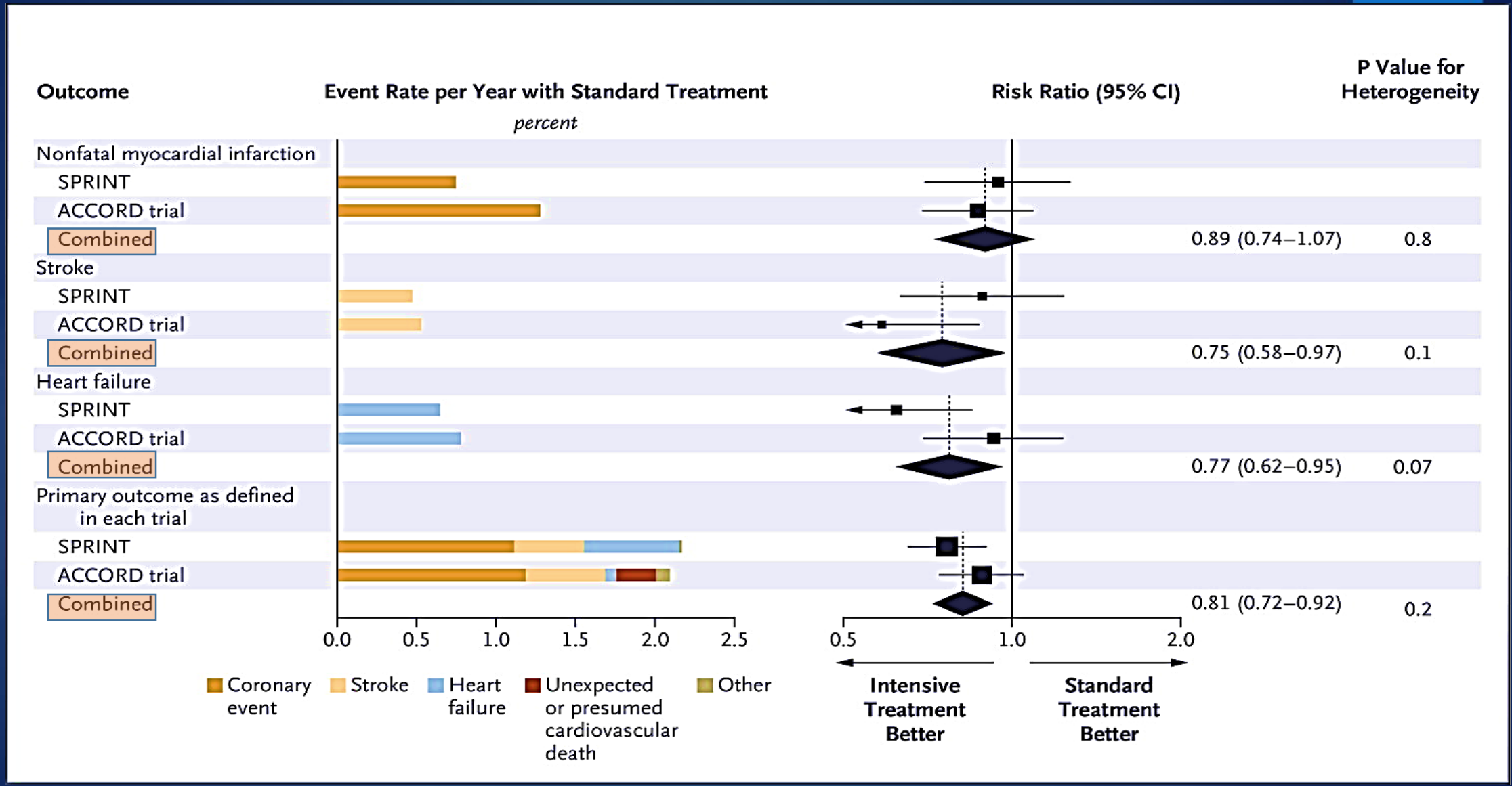
Serious Adverse Events* (SAE) During Follow-up

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

	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)

Wright et.al. N.Engl.J.Med. 2015;373 : 2103-2116

Outcomes from SPRINT and ACCORD Trials and Combined Data from Both Trials



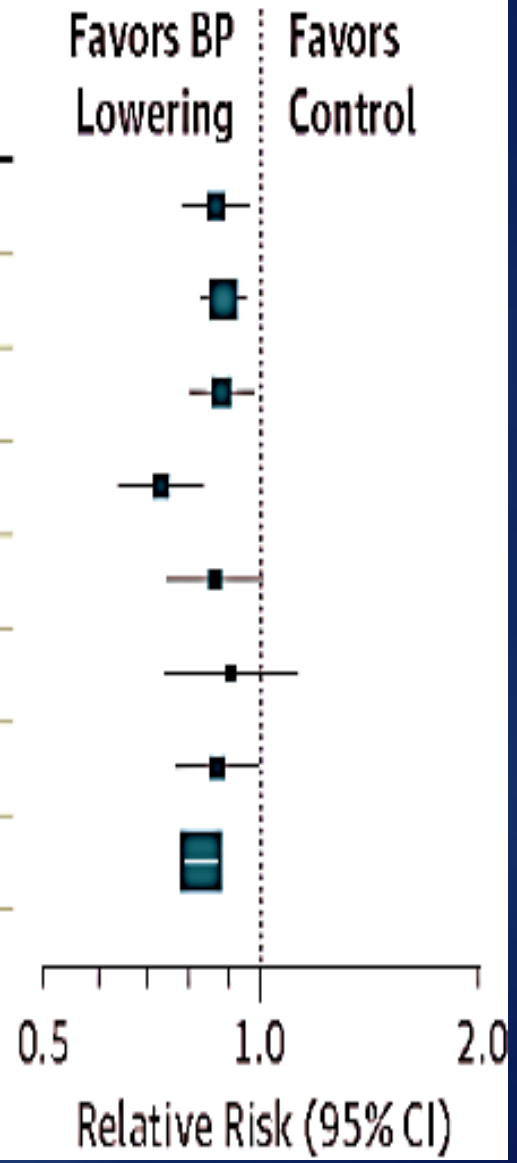
Perkovic V, Rodgers A. N Engl J Med 2015. DOI: 10.1056/NEJMe1513301

The NEW ENGLAND JOURNAL of MEDICINE

Standardized Associations Between 10–mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes in Patients with Diabetes

Outcome	No. of Studies	BP Lowering		Control		Relative Risk (95% CI)
		Events	Participants	Events	Participants	
Mortality	20	2334	27693	2319	25864	0.87 (0.78-0.96)
Cardiovascular disease	17	3230	25756	3280	24862	0.89 (0.83-0.95)
Coronary heart disease	17	1390	26150	1449	24761	0.88 (0.80-0.98)
Stroke	19	1350	27614	1475	26447	0.73 (0.64-0.83)
Heart failure	13	1235	21684	1348	20791	0.86 (0.74-1.00)
Renal failure	9	596	19835	560	18912	0.91 (0.74-1.12)
Retinopathy	7	844	9781	905	9566	0.87 (0.76-0.99)
Albuminuria	7	2799	13804	3163	12821	0.83 (0.79-0.87)

40 trials judged to be of low risk of bias (100 354 participants)



Emdin et.al. JAMA. 2015;313(6):603-615.

Should People with Diabetes be Included for a Lower BP Goal?

- Yes:
  - ACCORD HTN was underpowered
  - ACCORD 4,733 vs 9,361 in SPRINT
  - Strokes were significantly reduced in ACCORD
  - All other endpoints trended the right direction
- Longer follow-up showed significant reduction of primary endpoint and stroke
- ACCORDION extended follow-up for another 5 years
  - In 3957 pts of the standard Rx group intensive BP lowering resulted in
    - 21% reduction of CV events (P=0.001) and
    - test of interaction became significant (P=0.037)

Cushman, Bakris, AHA

Summary-Conclusions

In SPRINT, intensive therapy resulted in:

- 25% lower primary outcome (driven by heart failure events) and
- 27% reduction of all-cause mortality compared to standard group
- Treatment effect similar in all six prespecified groups
- The “number needed to treat” to prevent one event was:
- 61 for primary outcome event and 90 for any death
- In participants with CKD at baseline, no differences in renal outcomes were noted
- No overall difference in serious adverse events (SAEs) between treatment groups
- Target BP around 120 mmHg should be recommended for all high-risk patients with hypertension (who can tolerate it) as well as for most people with DM
- Caution needed for older people with competing risks and/or fragile patients

Wright, JT Jr., et.al. N Engl.J Med 373 (22):2103-2116, 2015.

New Wording in UpToDate Effective Jan 2016

- The following recommendation for goal blood pressure (BP) is for patients with increased risk of a CV event defined as those with age ≥ 75 years, clinically evident CV disease, an estimated glomerular filtration rate of 20 to 59 mL/min/1.73 m^2, or a 10-year Framingham Risk Score ≥ 15 percent.

New Wording in UpToDate

- This recommendation depends on the method used to determine BP. The ausculatory method using a manual cuff is the most common employed in clinical practice and, in addition, was the technique used in most clinical trials of antihypertensive therapy. **In contrast,** automated oscillometric BP (AOBP), using a device that can take multiple consecutive readings with the patient resting alone in a room, is infrequently employed in clinical practice but *was the technique used in SPRINT. In genera*l, systolic pressure readings are 5 to 10 mmHg lower with AOBP than with manual (ausculatory) measurement.
- For patients with one or more of the characteristics listed above, we recommend targeting a BP of 120 to 125/<90 mmHg rather than <140/<90 mmHg if AOBP measurements are used rather than a higher goal BP (**Grade 1A**). For these patients, we recommend targeting a BP of 125 to 130/<90 mmHg rather than <140/<90 mmHg if other methods of BP measurement are used.

www.UpToDate.com 2016

New Wording in UpToDate (cont.)

- In patients with diabetes, we suggest a goal blood pressure of 120 to 125/<90 mmHg (if automated oscillometric blood pressure readings are used to measure blood pressure), or a goal blood pressure of 125 to 130/<90 mmHg (if manual ausculatory measurements are used), rather than a goal blood pressure of <140/<90 mmHg (using manual ausculatory measurements) (Grade 2B).
- This suggestion is based upon data from various goal blood pressure trials in diabetic patients, plus indirect data from SPRINT (that included patients who, like those with diabetes, have a high cardiovascular risk)

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