SPRINT: Consequences for CKD patients

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Objectives

Weigh the risks and benefits of strict control of systolic blood pressure in patients with CKD

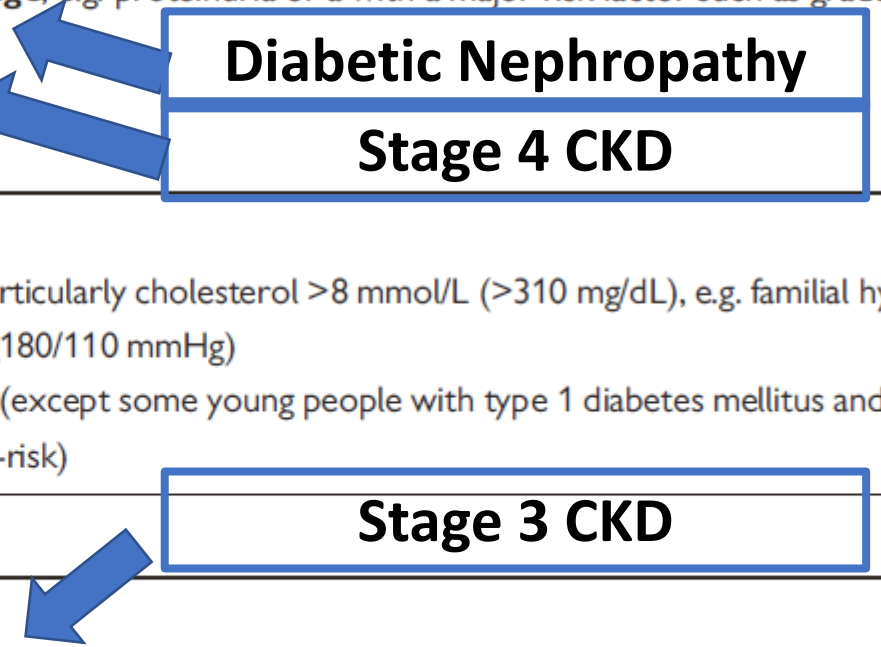
Understand how new data supports a lower blood pressure goal in the elderly

Reconcile the “differences” between the SPRINT and ACCORD results

Evaluate the severity and recovery of acute kidney injury in SPRINT

Ten year CV risk categories in SCORE

Very high risk	**People with any of the following:**
	Documented CVD, either clinical or unequivocal on imaging. • **Clinical CVD** includes acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, and PAD • **Unequivocal documented CVD on imaging** includes significant plaque (i.e. ≥50% stenosis) on angiography or ultrasound; it does not include increase in carotid intima-media thickness • **Diabetes mellitus with target organ damage**, e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia • **Severe CKD** (eGFR <30 mL/min/1.73 m^2) • **A calculated 10 year SCORE of ≥10%**
High risk	**People with any of the following:** • **Marked elevation of a single risk factor**, particularly cholesterol >8 mmol/L (>310 mg/dL), e.g. familial hypercholesterolaemia or grade 3 hypertension (BP ≥180/110 mmHg) • **Most other people with diabetes mellitus** (except some young people with type 1 diabetes mellitus and without major risk factors, who may be at moderate-risk)
	Hypertensive LVH
	Moderate CKD eGFR 30-59 mL/min/1.73 m^2)
	A calculated 10 year SCORE of 5-10%



Hypertension disease staging

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP 160–179 DBP 100–109	Grade 3 SBP ≥180 or DBP ≥110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

©ESC/ESH 2018

Risk for middle aged male

2018 ESC/ESH guidelines for management of arterial hypertension. European Heart Journal 39:3-021-3104, 2018.

ESC/ESH BP Thesholds for treatment

Table 19 Summary of office blood pressure thresholds for treatment

Age group	Office SBP treatment threshold (mmHg)					Office DBP treatment threshold (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/TIA	
18 - 65 years	≥140	≥140	≥140	≥140[a]	≥140[a]	≥90
65 - 79 years	≥140	≥140	≥140	≥140[a]	≥140[a]	≥90
≥80 years	≥160	≥160	≥160	≥160	≥160	≥90
Office DBP treatment threshold (mmHg)	≥90	≥90	≥90	≥90	≥90	

2018 ESC/ESH guidelines for management of arterial hypertension. European Heart Journal 39:3-021-3104, 2018.

ESC/ESH Office blood pressure target range

Table 23 Office blood pressure treatment target range

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke[a]/TIA	
18 - 65 years	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	**Target to <140 to 130** *if tolerated*	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	70–79
65 - 79 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
≥80 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
Office DBP treatment target range (mmHg)	70–79	70–79	70–79	70–79	70–79	

2018 ESC/ESH guidelines for management of arterial hypertension. European Heart Journal 39:3-021-3104, 2018.

Differences in ACC/AHA and ESC/ESH BP guidelines

	2017 ACC/AHA	2018 ESC/ESH
Classification of blood pressure status and definition of hypertension (office BP)	Stage 1 hypertension: SBP 130-139 mm Hg or DBP 80-89 mm Hg. Stage 2 hypertension: SBP ≥140 mm Hg or DBP ≥90 mm Hg.	High normal BP: SBP 130-139 mm Hg or DBP 80-89 mm Hg. Hypertension (Grade 1-3): SBP ≥140 mm Hg or DBP ≥90 mm Hg.
Lifestyle interventions **All patients with CKD stage 3 or 4** →	Core management for prevention and treatment of hypertension. Complemented by drug therapy for adults with stage 1 hypertension and a high risk of CVD (prior CVD event or 10-year risk of ASCVD risk ≥10%) Drug therapy for Stage 2 hypertension (≥140/90mmHg)	Predominantly lifestyle interventions for adults with high normal BP; only consider drug therapy for very high-risk patients. ↓ **Stage 4 CKD or diabetic nephropathy** Lifestyle interventions alone for uncomplicated low risk grade 1 hypertension for 3-6 months, with drug therapy thereafter if BP not controlled. ↓ **Stage 3 CKD, not diabetic**

Whelton PK, Williams B. *JAMA*. doi:10.1001/jama.2018.16755 [published November 6, 2018]

Differences in hypertension definition

- The definition of hypertension in the European guideline is unchanged, reflecting the level of BP (140/90 mmHg) at which drug treatment is recommended for all patients.
- In the US guideline, hypertension is defined by an average systolic BP of at least 130 mmHg or diastolic BP of 80 mmHg or higher, based on an interpretation of risk and treatment effect.
- This results in a different approach to treatment of adults with a systolic BP of 130 through 139 mmHg or diastolic BP of 80 through 89 mm Hg, who are classified as having stage 1 hypertension in the US guideline and high normal BP in the European guideline.

Treatment for SBP 130 – 139 mm Hg and DBP 80 – 89 mm Hg

- The US guideline recommends:
  - Nonpharmacological therapy for all adults with stage 1 hypertension
  - Additional antihypertensive drug therapy for the approximately 30% in this highly prevalent BP category who are deemed to be at high risk for atherosclerotic CVD (10-year risk of atherosclerotic CVD ≥10%). This includes all patients with CKD stages 3-5.
- In contrast, the European guideline predominantly recommends lifestyle interventions, with consideration of antihypertensive drug therapy only in adults at very high risk, i.e., with established CVD, especially coronary artery disease.

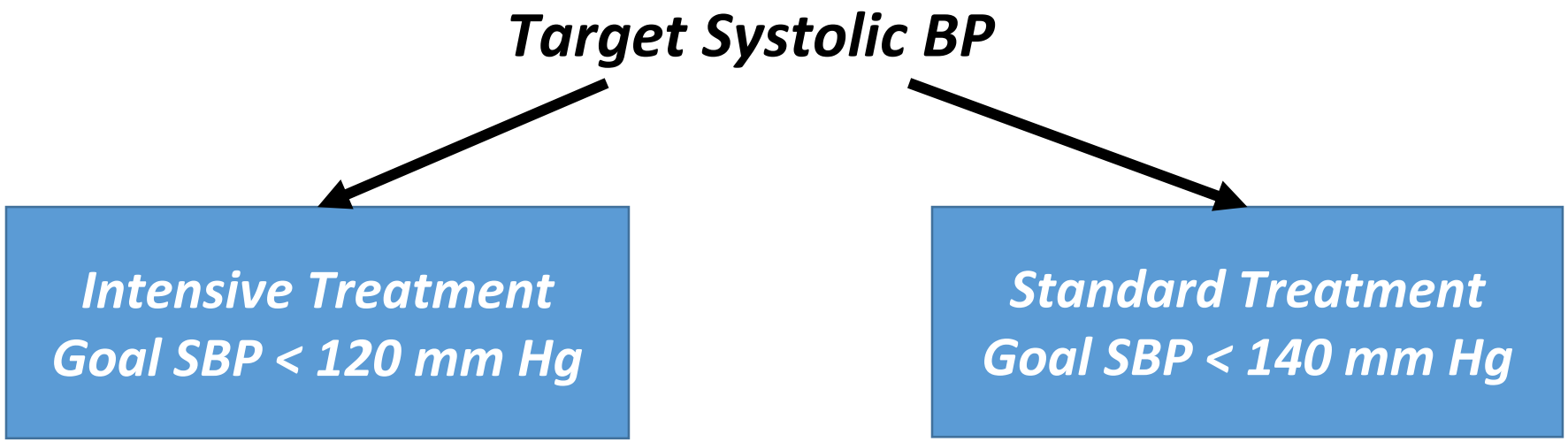
Differences in ACC/AHA and ESC/ESH BP guidelines

	2017 ACC/AHA	2018 ESC/ESH
BP thresholds for intervention with BP-lowering drug therapy	SBP ≥130 mm Hg or DBP ≥80 mm Hg for adults at high risk for CVD (prior CVD event or 10-year ASCVD risk ≥10%).	SBP ≥140 mm Hg or DBP ≥90 mm Hg for all adults up to age of 80 years. SBP ≥160 mm Hg or DBP ≥90 mm Hg for adults aged >80 years.(who have not yet received treatment) Treatment may be considered in adults with high normal BP who are at very high risk due to established CVD, especially coronary artery disease.
BP targets for treatment	SBP <130 mm Hg and DBP <80 mm Hg for all adults, except those ≥65 years where target should be an SBP <130 mm Hg.	SBP 130 mm Hg or lower but not <120 mm Hg in adults 18-65 years. Less aggressive targets in adults aged >65 years – SBP target range <140 – 130 mm Hg if tolerated, but not usually <130 mm Hg.

Whelton PK, Williams B. *JAMA*. doi:10.1001/jama.2018.16755 [published November 6, 2018]

SPRINT Research Question

Randomized controlled clinical trial to examine effect of more intensive high blood pressure treatment strategy than is currently recommended (standard treatment)



SPRINT design details available at ClinicalTrials.gov (NCT01206062)
Ambrosius WT et al. Clin Trials. 2014;11:532-546.

Major Inclusion Criteria

- 50 years of age or older
- Systolic blood pressure: 130 – 180 mm Hg (treated or untreated)
- At least one additional cardiovascular disease (CVD) risk factor
  - Clinical or subclinical CVD (excluding stroke)
  - Chronic kidney disease (CKD), defined as eGFR between 20 and 59 ml/min/1.73m^2
  - Framingham Risk Score for 10-year CVD risk ≥ 15%
  - Age ≥ 75 years

Major Exclusion Criteria

- Stroke
- Diabetes mellitis (ACCORD)
- Polycystic kidney disease (HALT-PKD)
- Congestive heart failure (symptoms or EF < 35%)
- Proteinuria >1 gram/day
- CKD with eGFR < 20 mL/min/1.73m^2 (MDRD)
- Adherence concerns

SPRINT Results in CKD cohort

CLINICAL RESEARCH www.jasn.org

Effects of Intensive BP Control in CKD

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Lower SBP goal in CKD subgroup – also show reduced rates of CVD and death

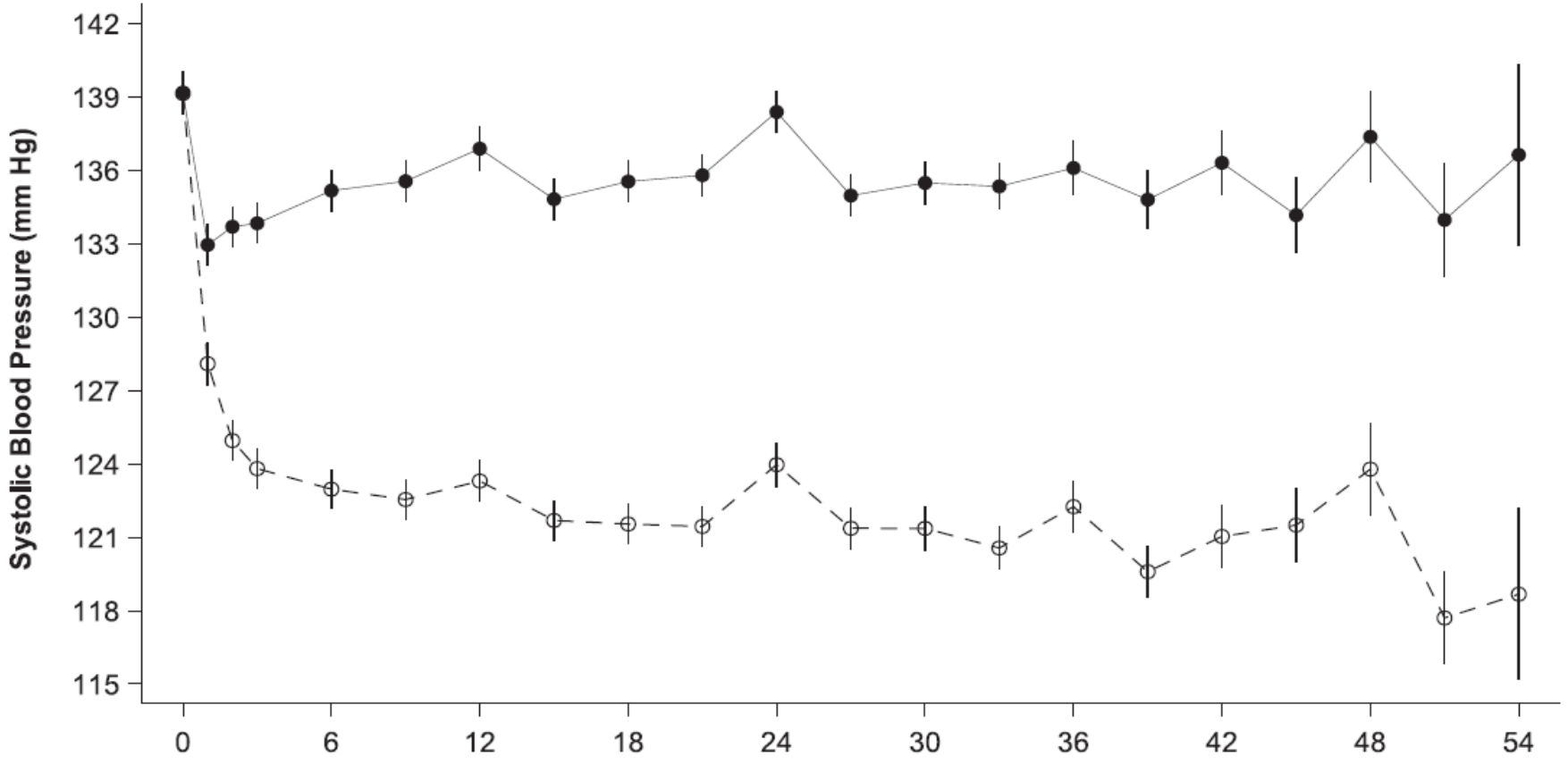
...appropriate target for BP in patients with CKD and hypertension remains uncertain. We report pre-specified subgroup analyses of outcomes in participants with baseline CKD in the Systolic Blood Pressure Intervention Trial. We randomly assigned participants to a systolic BP target of <120 mm Hg (intensive group; *n*=1330) or <140 mm Hg (standard group; *n*=1316). After a median follow-up of 3.3 years, the primary composite cardiovascular outcome occurred in 112 intensive group and 131 standard group CKD participants (hazard ratio [HR], 0.81; 95% confidence interval [95% CI], 0.63 to 1.05). The intensive group also had a lower rate of all-cause death (HR, 0.72; 95% CI, 0.53 to 0.99). Treatment effects did not differ between participants with and without CKD (*P* values for interactions ≥0.30). The prespecified main kidney

Baseline characteristics of SPRINT participants with CKD

Characteristics	Intensive treatment (n=1330)	Standard treatment (n=1316)	Total (n=2646)
Age, mean + SD (year)	72.0 ± 9.0	71.9 ± 9.5	71.9 ± 9.3
Age ≥75 years, no. (%)	584 (43.9)	577 (43.8)	1161 (43.9)
Women, no. (%)	537 (40.4)	521 (39.6)	1058 (40.0)
Serum creatinine, mg/dl	1.43 (0.39)	1.43 (0.38)	1.43 (0.39)
eGFR, mean (SD), ml/min per $1.73m^2$	47.9 (9.5)	47.9 (9.5)	47.9 (9.5)
Urinary ACR (median (interquartile range)	12.8 (6.5 – 42.6)	13.8 (6.1 – 43.5)	13.3 (6.4 – 43.1)

Cheung AK et al. J Am Soc Nephrol 28:2812-2823, 2017

Blood pressure during SPRINT follow-up



	Number With Data									
Standard:	1316	1215	1156	1117	1087	1022	766	480	230	46
Intensive:	1330	1246	1194	1145	1136	1054	804	515	268	58
	Mean Number of Meds									
Standard:	2.1	2.0	2.0	2.0	2.1	2.0	2.1	2.1	2.1	2.0
Intensive:	2.1	2.9	3.0	3.0	3.0	3.0	2.9	2.9	3.0	3.1

Cheung AK et al. J Am Soc Nephrol. 28: 2812-2823, 2017

Number of anti-hypertensive medications

Medication Usage	Intensive Treatment, *n*=1330	Standard Treatment, *n*=1316
No. of medications		
Mean no. of medications (SD)	2.90 (1.24)	2.02 (1.23)
Zero medications, no. (%)	25 (1.9)	123 (9.3)
One medication, no. (%)	124 (9.3)	359 (27.3)
Two medications, no. (%)	376 (28.3)	399 (30.3)
Three medications, no. (%)	398 (29.9)	278 (21.1)
Four or more medications, no. (%)	407 (30.6)	157 (11.9)

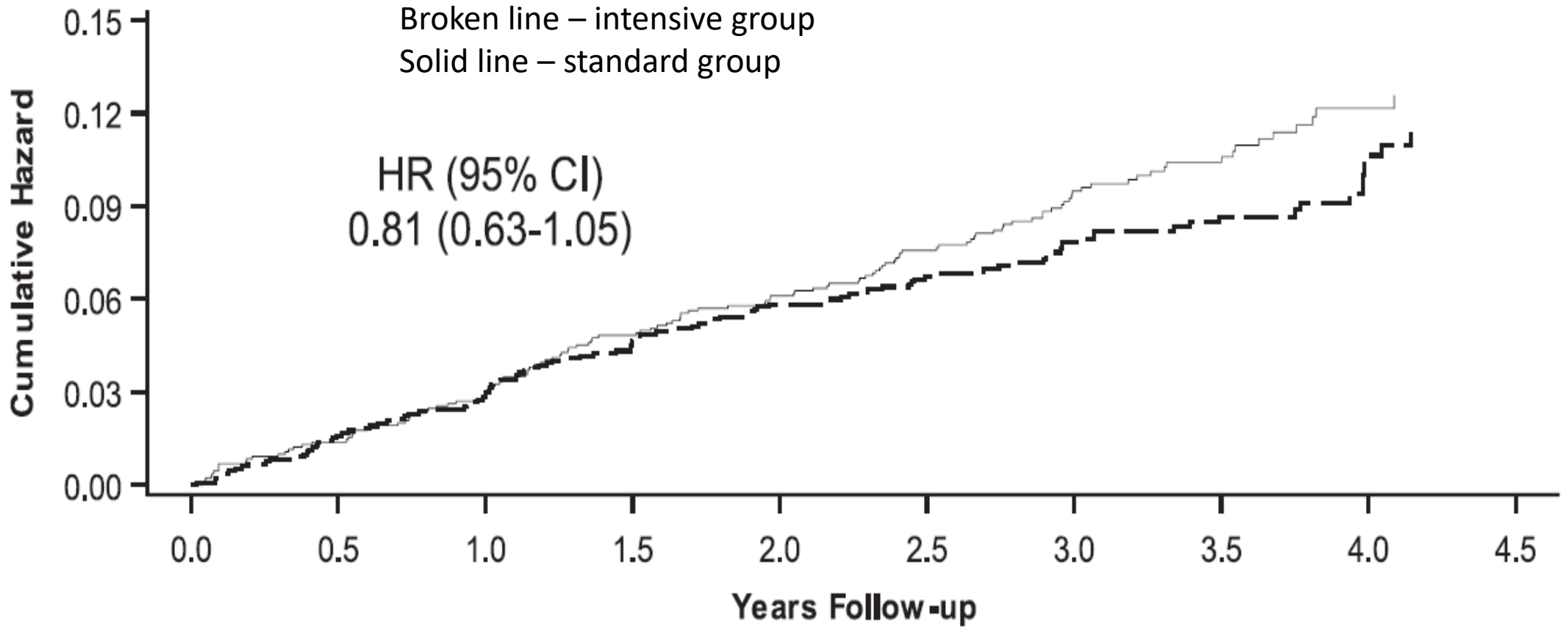
Cheung AK et al. J Am Soc Nephrol. 28: 2812-2823, 2017

Anti-hypertensive medications by type

Medication	Intensive treatment; n = 1330	Standard treatment; n = 1316
RAS blockers	71.7%	57.0%
ACE-I	35.4%	30.1%
ARBs	36.2%	27.0%
Diuretics	67.3%	46.6%
Thiazide	46.8%	30.1%
Loop	18.7%	15.2%
Alpha-1 blockers	12.9%	6.7%
Calcium channel blockers	60.9%	37.3%
Direct vasodilators	11.5%	4.2%
Beta-blockers	53.3%	42.2%

Cheung AK et al. J Am Soc Nephrol. 28: 2812-2823, 2017

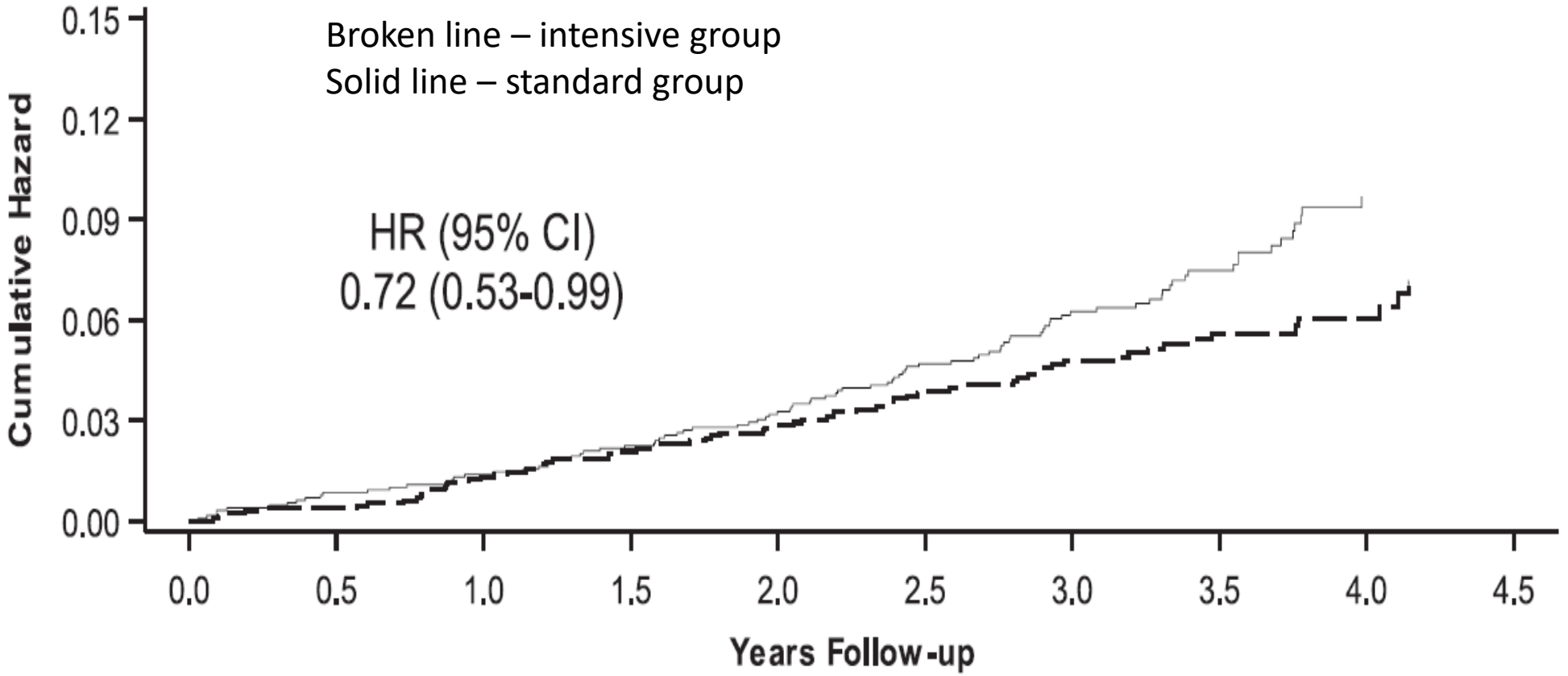
Kaplan Meier curve for primary cardiovascular outcome – SPRINT CKD



Number at risk					
Standard	1316	1241	1164	801	245
Intensive	1330	1243	1181	808	278

Cheung AK et al. J Am Soc Nephrol 28:2812-2823, 2017

Kaplan Meier curve for all cause death - SPRINT CKD cohort



Number at risk

Standard	1316	1277	1227	865	269
Intensive	1330	1279	1244	859	295

Cheung AK et al. J Am Soc Nephrol 28:2812-2823, 2017

SAEs and conditions of interest – SPRINT CKD

Events	No. of Events (% per 1 yr)		Intensive Treatment Versus Standard Treatment	
	Intensive Treatment, *n*=1330	Standard Treatment, *n*=1316	HR (95% CI)	*P* Value
Total SAEs[a]	627 (19.8)	640 (20.2)	0.98 (0.87 to 1.09)	0.67
Conditions of interest (emergency department visits or SAEs)				
Hypotension	51 (1.2)	38 (0.9)	1.34 (0.88 to 2.04)	0.17
Syncope	54 (1.3)	42 (1.0)	1.28 (0.86 to 1.92)	0.22
Bradycardia	37 (0.9)	40 (1.0)	0.92 (0.59 to 1.44)	0.71
Electrolyte abnormalities	69 (1.7)	51 (1.2)	1.35 (0.94 to 1.94)	0.10
Injurious fall	125 (3.1)	138 (3.4)	0.90 (0.71 to 1.15)	0.40
ARF[b]	114 (2.8)	78 (1.9)	1.46 (1.10 to 1.95)	0.01

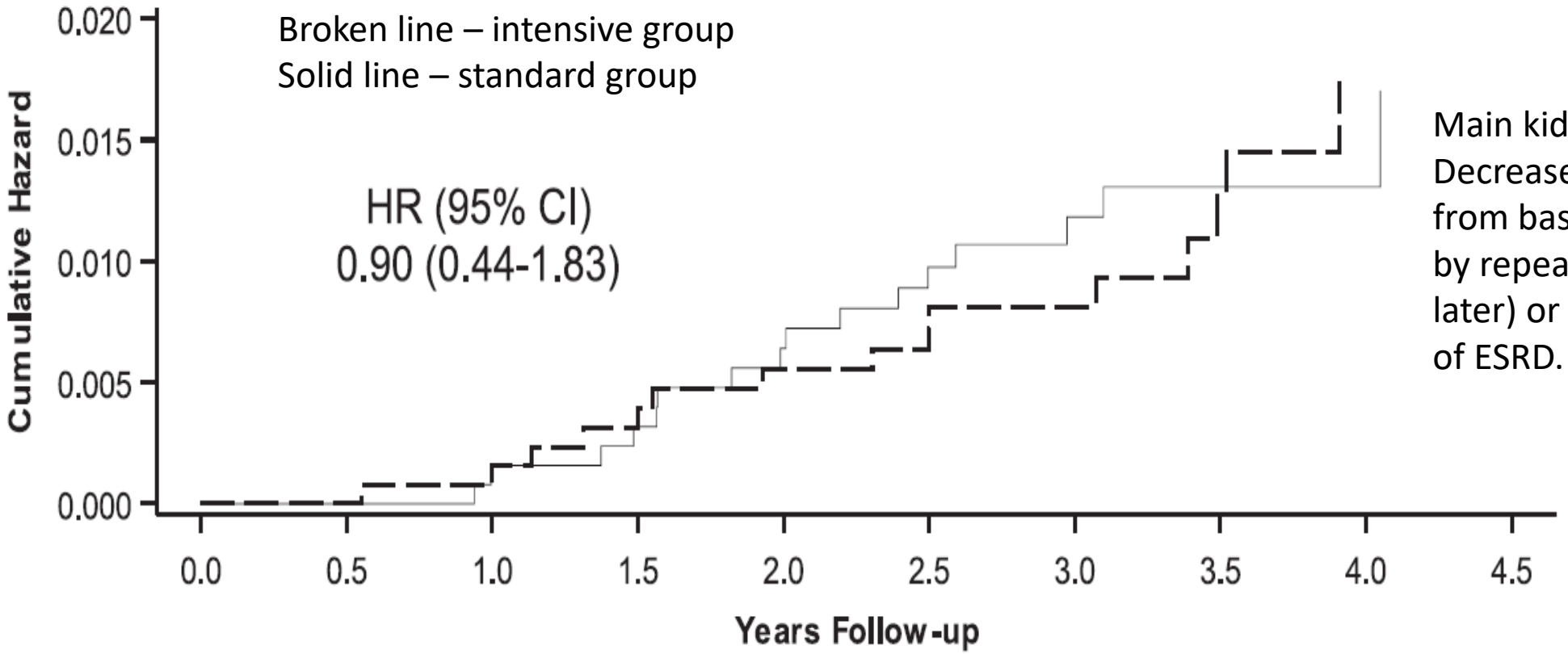
Cheung AK et al. J Am Soc Nephrol. 28: 2812-2823, 2017

Monitored clinical events – SPRINT CKD

Events	No. of Events (% per 1 yr)		Intensive Treatment Versus Standard Treatment	
	Intensive Treatment, *n*=1330	Standard Treatment, *n*=1316	HR (95% CI)	*P* Value
Monitored clinical events				
Adverse clinical measures				
Serum sodium <130 mmol/L	49 (2.7)	35 (0.9)	1.39 (0.90 to 2.15)	0.13
Serum sodium >150 mmol/L	3 (0.1)	0 (0)	—	>0.99
Serum potassium <3.0 mmol/L	30 (0.7)	16 (0.4)	1.87 (1.02 to 3.43)	0.04
Serum potassium >5.5 mmol/L	106 (2.7)	78 (2.0)	1.36 (1.01 to 1.82)	0.04
Orthostatic hypotension				
Without dizziness	301 (8.5)	302 (8.5)	0.99 (0.85 to 1.17)	0.94
With dizziness	24 (0.6)	23 (0.6)	1.04 (0.59 to 1.84)	0.89

Cheung AK et al. J Am Soc Nephrol. 28: 2812-2823, 2017

Kaplan Meier curve for main kidney outcome – SPRINT CKD cohort

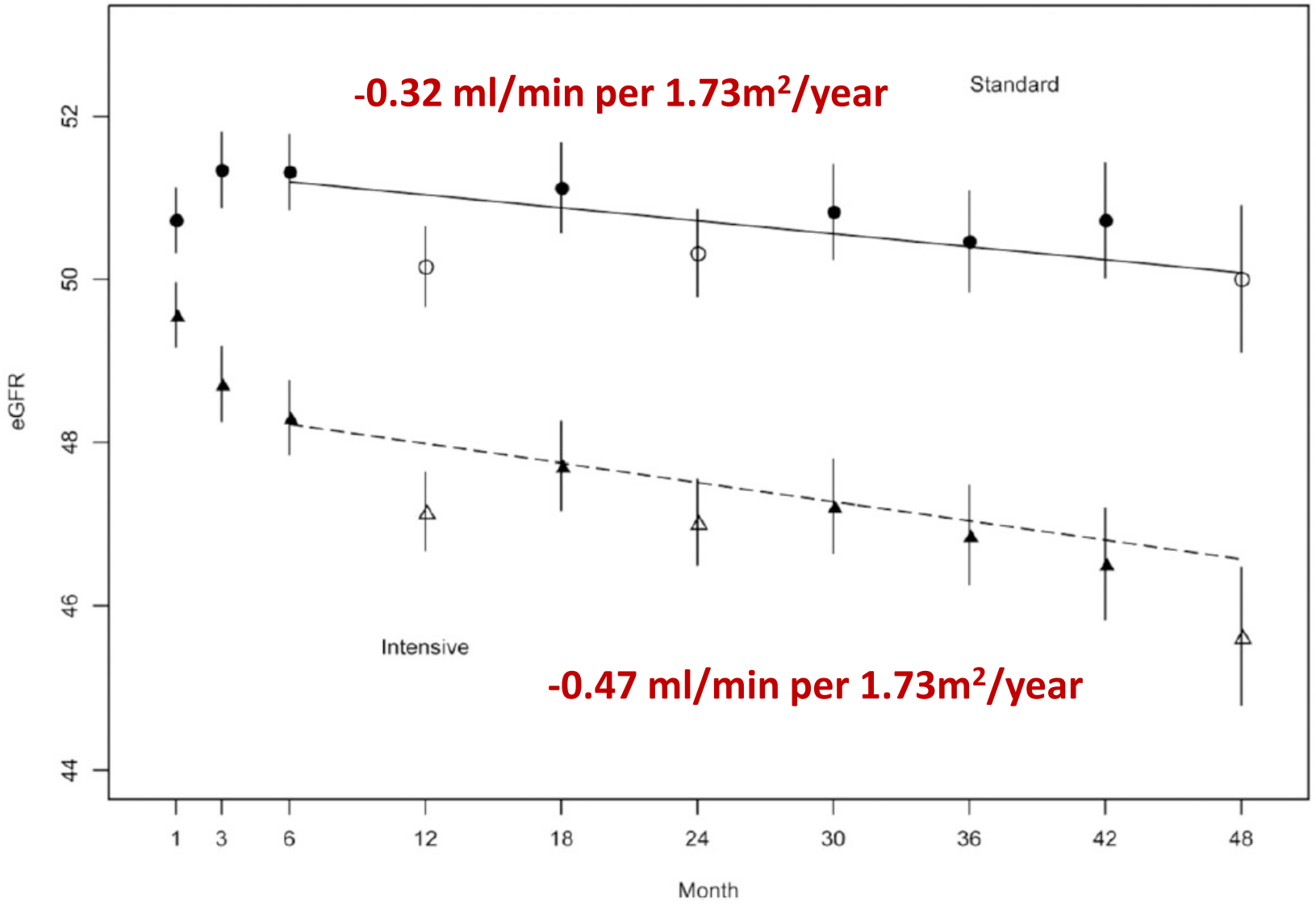


Number at risk					
Standard	1316	1265	1214	854	266
Intensive	1330	1268	1230	850	286

Main kidney outcome: Decrease in eGFR of ≥50% from baseline (confirmed by repeat testing ≥90 days later) or the development of ESRD.

Cheung AK et al. J Am Soc Nephrol 28:2812-2823, 2017

Change in eGFR in SPRINT CKD participants



Open symbols – fasting creatinine values

Closed symbols – non-fasting values

Difference in slopes after 6 months:
p = 0.03

Cheung AK et al. J Am Soc Nephrol. 28: 2812-2823, 2017

Urinary kidney biomarkers in the SPRINT CKD cohort

- Random sample of 978 SPRINT participants with prevalent chronic kidney disease (CKD) defined as eGFR < 60 mL/min/1.73 m^2 by the CKD-EPI (CKD Epidemiology Collaboration) creatinine-cystatin C equation at baseline.
- Urine biomarkers were measured at baseline and years 1 and 4
- Tubular reabsorption
  - β2-microglobulin [β2M], α1-microglobulin [α1M]),
  - Serum proteins that are filtered by the glomerulus and then reabsorbed by the proximal tubule
- Synthesized solely by the proximal tubule
  - Uromodulin (UMOD)

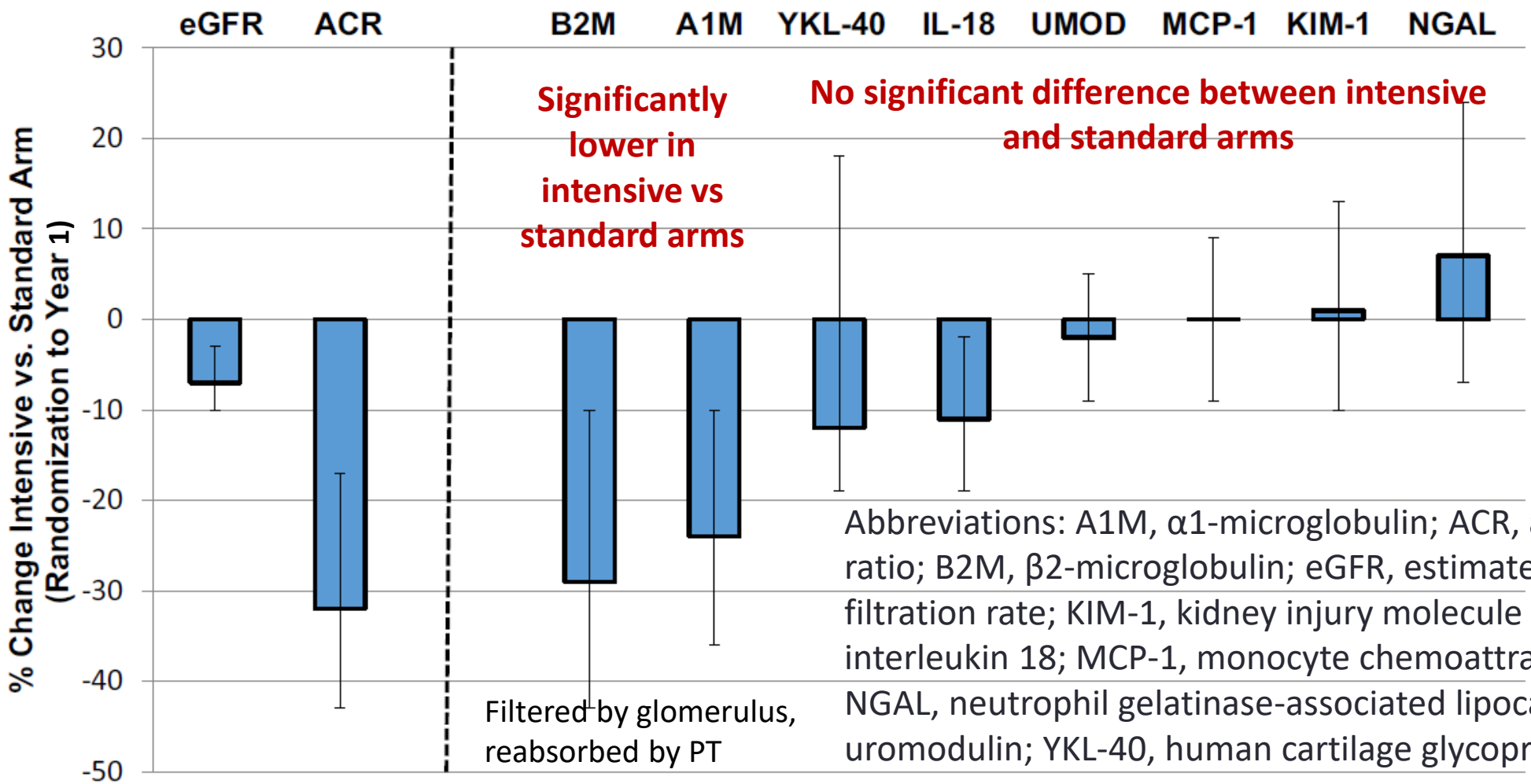
Malhotra R et al. AJKD 2018 (in press) https://doi.org/10.1053/j.ajkd.2018.07.015

Urinary biomarker characteristics

- The other 6 urinary tubule biomarkers are produced in kidney tissue in response to damage, inflammation, and repair and are not known to be filtered at the glomerulus.
- Tubular injury
  - Interleukin 18 (IL-18), kidney injury molecule 1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL)
- Tubular inflammation
  - Monocyte chemoattractant protein 1 (MCP-1)
- Tubular repair
  - Human cartilage glycoprotein 40 (YKL-40)

Malhotra R et al. AJKD 2018 https://doi.org/10.1053/j.ajkd.2018.07.015

Change in urinary biomarkers in CKD cohort; percent change at year 1



Abbreviations: A1M, α1-microglobulin; ACR, albumin-creatinine ratio; B2M, β2-microglobulin; eGFR, estimated glomerular filtration rate; KIM-1, kidney injury molecule 1; IL-18, interleukin 18; MCP-1, monocyte chemoattractant protein 1; NGAL, neutrophil gelatinase-associated lipocalin; UMOD, uromodulin; YKL-40, human cartilage glycoprotein 39.

Malhotra R et al. AJKD 2018 https://doi.org/10.1053/j.ajkd.2018.07.015

Urinary biomarker conclusions

- None of the 8 tubule marker levels was higher in the intensive arm compared to the standard arm at year 4.
- Only two tubule function markers were lower at year 1 in the intensive versus standard arm, respectively
  - β_2 microglobulin was 29% lower (95% CI, 10%-43%)
  - α_1 microglobulin was 24% lower (95% CI, 10%-36%)
- Thus, intensive SBP lowering results in a hemodynamic decrease in GFR, which not only lowers creatinine filtration, but also lowers β2M and α1M filtration in the presence of preserved tubular absorptive capacities, resulting in lower urine concentrations

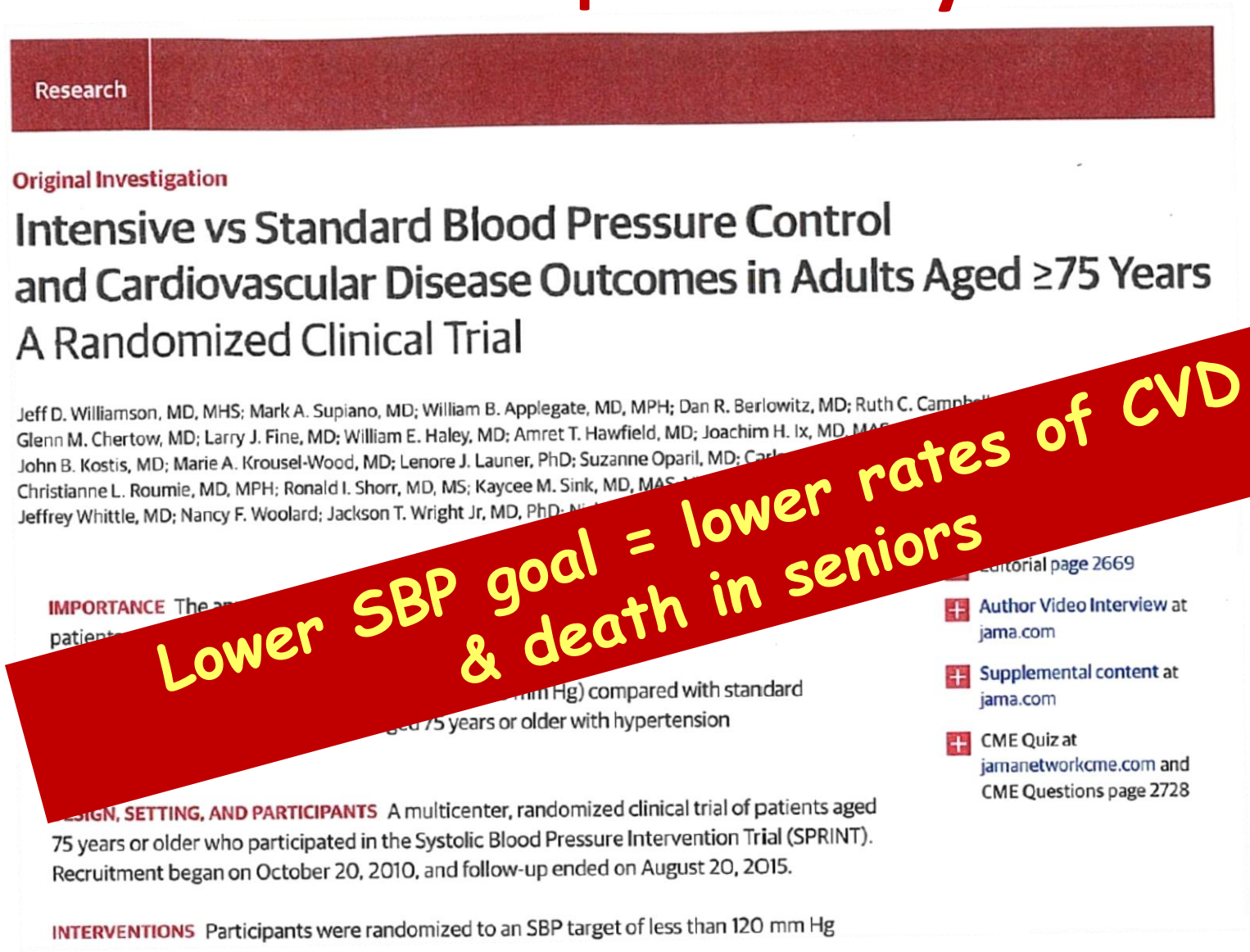
Malhotra R et al. AJKD 2018 https://doi.org/10.1053/j.ajkd.2018.07.015

Urinary biomarker study implications

- Because higher urine levels of these kidney tubule markers have been linked to CKD progression, dialysis therapy initiation, and adverse health outcomes, the present results provide reassurance that the eGFR decline with intensive BP lowering is likely predominantly hemodynamic in nature.
- These findings support, but do not prove, the hypothesis that hemodynamic effects on eGFR may persist for years without necessarily causing tubule damage.
- In addition, our findings suggest that the tubule health markers may have utility to assess intrinsic versus hemodynamic changes in kidney function in other settings that are known to influence renal perfusion.

Malhotra R et al. AJKD 2018 https://doi.org/10.1053/j.ajkd.2018.07.015

SPRINT in Participants ≥75 years



Research

Original Investigation

Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years
A Randomized Clinical Trial

Jeff D. Williamson, MD, MHS; Mark A. Supiano, MD; William B. Applegate, MD, MPH; Dan R. Berlowitz, MD; Ruth C. Campbell
Glenn M. Chertow, MD; Larry J. Fine, MD; William E. Haley, MD; Amret T. Hawfield, MD; Joachim H. Ix, MD, MAS
John B. Kostis, MD; Marie A. Krousel-Wood, MD; Lenore J. Launer, PhD; Suzanne Oparil, MD; Carl
Christianne L. Roumie, MD, MPH; Ronald I. Shorr, MD, MS; Kaycee M. Sink, MD, MAS
Jeffrey Whittle, MD; Nancy F. Woolard; Jackson T. Wright Jr, MD, PhD; Ni

Lower SBP goal = lower rates of CVD & death in seniors

Editorial page 2669

Author Video Interview at jama.com

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and CME Questions page 2728

IMPORTANCE The
patient
mm Hg) compared with standard
75 years or older with hypertension

DESIGN, SETTING, AND PARTICIPANTS A multicenter, randomized clinical trial of patients aged 75 years or older who participated in the Systolic Blood Pressure Intervention Trial (SPRINT). Recruitment began on October 20, 2010, and follow-up ended on August 20, 2015.

INTERVENTIONS Participants were randomized to an SBP target of less than 120 mm Hg

Williamson, JD et al. JAMA 315: 2673-2682, 2016

SPRINT Results in Participants ≥75 years

- Mean age, 79.9 years; 37.9% women, n = 2560
- There was a significantly lower rate of the primary composite outcome:
  - 102 events in the intensive treatment group
  - 148 events in the standard treatment group
  - Hazard ratio [HR], 0.66 [95% CI, 0.51 - 0.85]

  and in all-cause mortality
  - 73 deaths (intensive arm) vs 107 deaths (Standard arm)
  - HR, 0.67 [95% CI, 0.49 - 0.91]
- The overall rate of serious adverse events was not different between treatment groups
  - 48.4% in the intensive treatment group vs
  - 48.3% in the standard treatment group;
  - HR, 0.99 [95% CI, 0.89 - 1.11]

Williamson, JD et al. JAMA 315: 2673-2682, 2016

SPRINT in participants ≥75 years

Research

JAMA Internal Medicine | Original Investigation

Effect of Intensive Blood Pressure Control on Gait Speed and Mobility Limitation in Adults 75 Years or Older
A Randomized Clinical Trial

Michelle C. Odden, PhD; Carmen A. Peralta, MD; Dan R. Berlowitz, MD; Karen C. Johnson, ...
Jeffrey Whittle, MD; Dalane W. Kitzman, MD; Srinivasan Beddhu, MD; John W. ...
Vasilios Papademetriou, MD; Jeff D. Williamson, MD; Nicholas M. ...
Intervention Trial (SPRINT) Research Group

Supplemental content

...ascular
...ies is unknown.

...e BP control on changes in gait speed and

...SETTING, AND PARTICIPANTS This randomized, clinical trial included 2636 individuals 75 years or older with hypertension and no history of type 2 diabetes or stroke who participated in the Systolic Blood Pressure Intervention Trial (SPRINT). Data were collected from November 8, 2010, to December 1, 2015. Analysis was based on intention to treat.

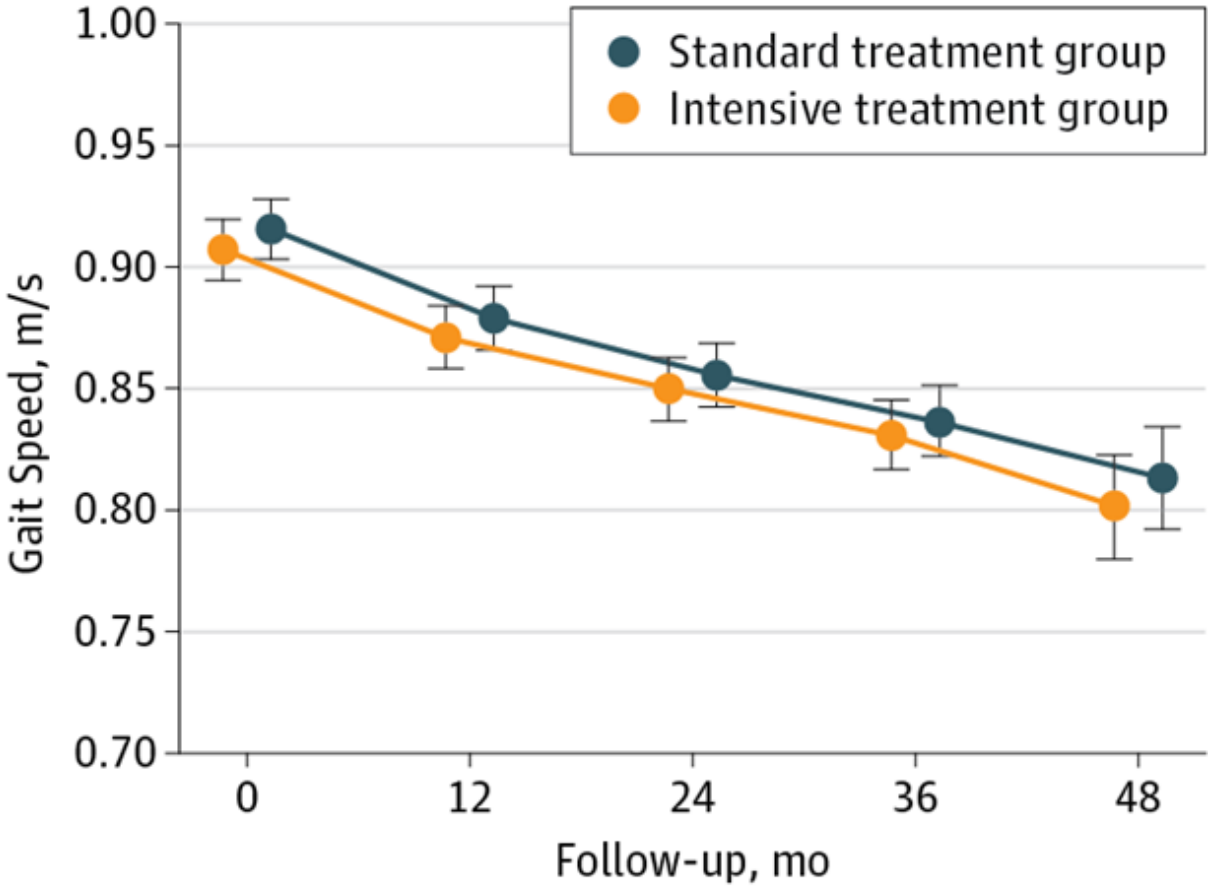
INTERVENTIONS Participants were randomized to intensive treatment with a systolic BP target of less than 120 mm Hg (n = 1317) vs standard treatment with a BP target of less than 140 mm Hg (n = 1319).

Lower SBP goal = no reduction in gait speed or mobility

Odden MC et al. JAMA Int Med 177: 500-507, 2017

Least squares mean for gait speed by treatment group

Circles denote estimated least mean square mean for gait speed based on linear mixed model. Error bars represent 95% confidence limits.



No. at risk					
Standard treatment group	1272	1150	1086	790	265
Intensive treatment group	1269	1160	1101	822	252

Odden MC et al. JAMA Int Med 177: 500-507, 2017

SPRINT and Risk of Mild Cognitive Impairment (MCI) and Dementia

- Treatment in SPRINT was stopped on 8/20/2015 due to cardiovascular disease (CVD) benefit after a median follow up of 3.26 years, but cognitive assessment continued until 6/29/2018.
- Participant mean age was 67.9 years (35.6% women) and 8,626 (92.1%) completed at least one follow-up cognitive assessment
- There was a significantly lower rate of adjudicated incident MCI (HR = 0.83, 95% CI: 0.71 to 0.97, p = 0.02)
- There was a non-significant reduction in probable dementia (HR = 0.84, 95% CI: 0.67 to 1.05, p = 0.12).
- The combined outcome of MCI plus probable all cause dementia was significantly lower (HR = 0.86, 95% CI: 0.75 to 0.99, p = 0.03) in the intensive *versus* standard treatment group.

Williamson JD et al. Alzheimer's Association International Conference 2018, Abstract #27525

SPRINT and Brain Structure

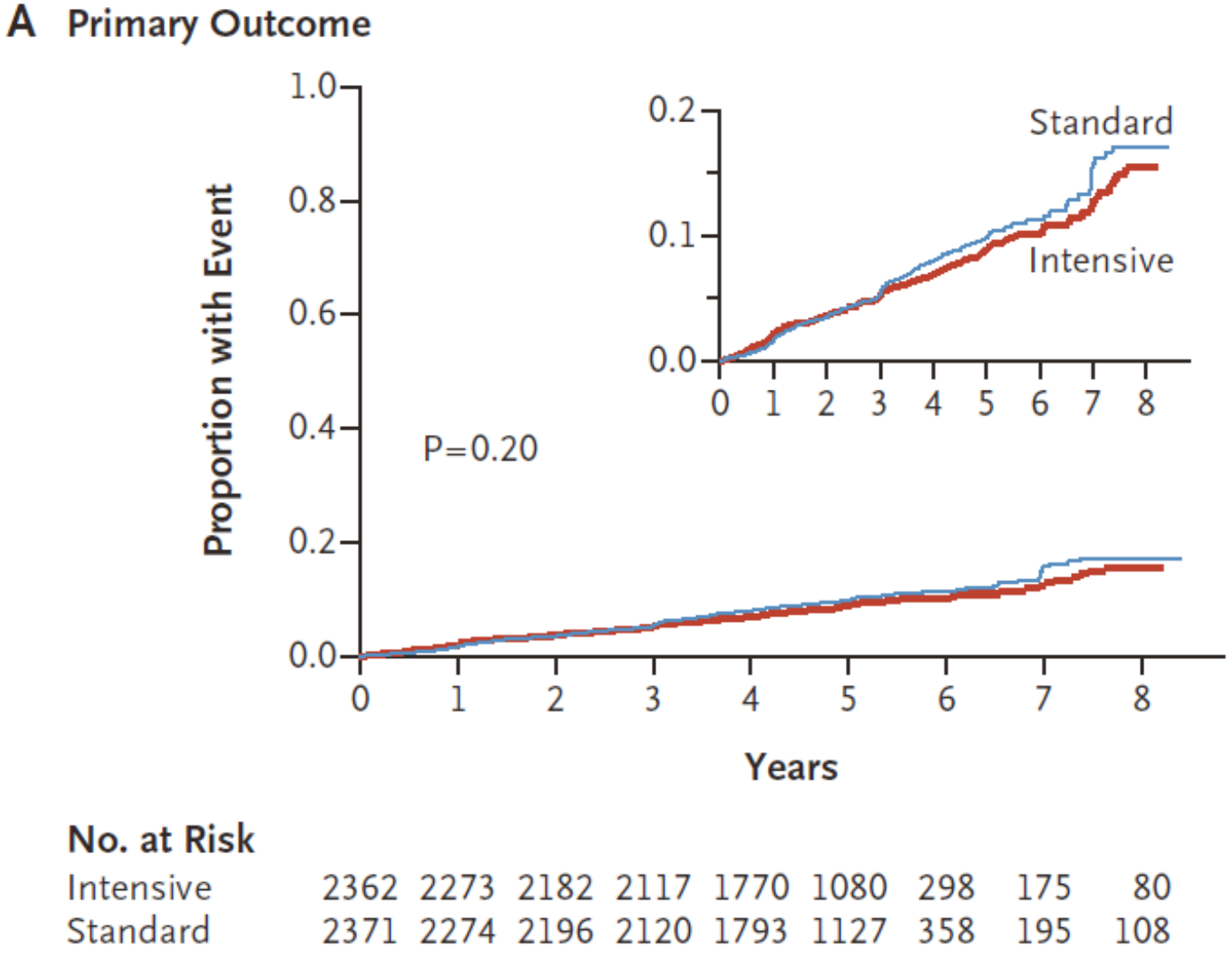
- 673 participants in the Systolic Blood Pressure Intervention Trial (SPRINT) were recruited for brain magnetic resonance imaging (MRI)
- Primary outcomes included change in total white matter lesion (WML) volume and total brain volume (TBV)
- Follow-up MRIs were obtained for 454 (67.4%) participants at a median of 3.98 years post-randomization.
- White matter lesion volume (WML)
  - Intensive arm: WML increased by 0.28 cm^3 (95% CI: -0.03 to 0.58)
  - Standard arm: WML increased by 0.92 cm^3 (95% CI: 0.59 to 1.24)
  - Mean difference = 0.64 cm^3, p = 0.004.
- Total brain volume (TBV)
  - Intensive arm: TBV decreased by 27.3 cm^3 (95% CI: 24.8 to 29.8)
  - Standard arm: TBV decreased by 24.8 cm^3 (95% CI: 22.0 to 27.5)
  - Mean difference = 2.54 cm^3, p = 0.16.

Nasrallah IM et al. Alzheimer's Association International Conference 2018, Abstract #27526

ACCORD Trial – BP control in patients with diabetes mellitus

- ACCORD-BP was a randomized, multicenter, 2 X 2 factorial clinical trial.
  - Patients were randomized to either an intensive BP control strategy (goal SBP < 120 mmHg) or a standard BP control strategy (goal SBP < 140 mmHg)
  - Patients also randomized to an intensive (hemoglobin A1c goal <6.0%) or standard glucose control strategy (hemoglobin A1c goal 7.0–7.9%).
- In the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORDBP) study, an intensive BP control strategy to achieve a systolic BP (SBP) <120 mmHg did not significantly reduce the composite of CVD death, nonfatal myocardial infarction, and nonfatal stroke compared with a standard SBP control goal of <140 mmHg

Primary outcome in ACCORD



The annual rate of the primary outcome was:

- 1.87% in the intensive-therapy group
- 2.09% in the standard-therapy group

Hazard ratio with intensive therapy is 0.88

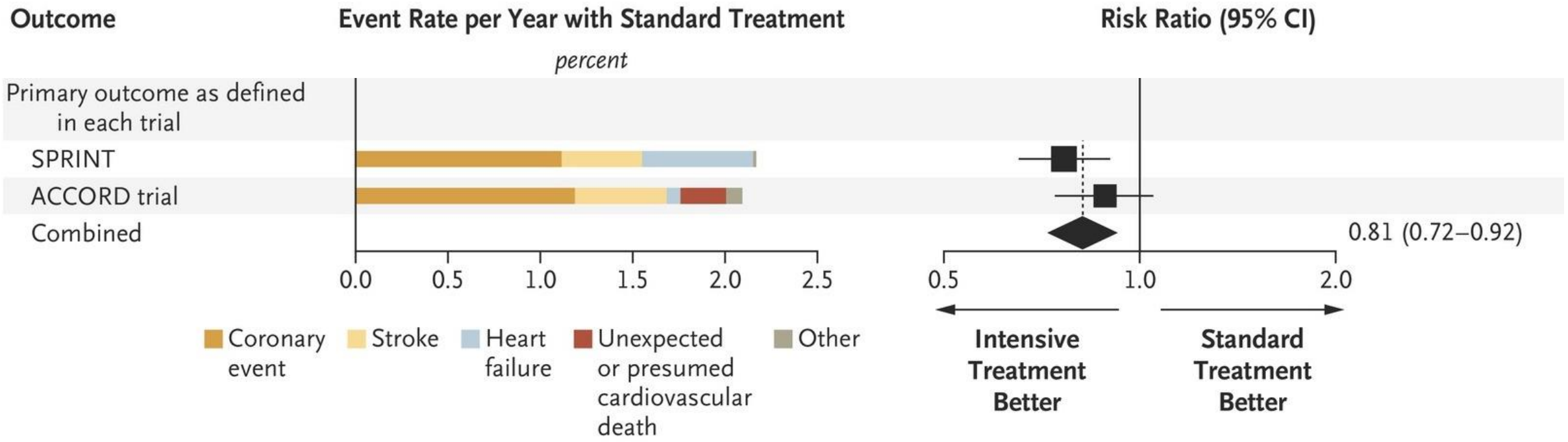
95% confidence interval [CI] 0.73 - 1.06; P = 0.20)

N Engl J Med 2010;362:1575-85.

Why do the ACCORD and SPRINT results differ?

- Multiple hypotheses have been proposed to explain the apparent discordance between these two studies.
- Given that the most notable difference in the patient populations was the absence of type 2 diabetes mellitus (T2DM) in SPRINT and the inclusion of T2DM in ACCORD-BP it is possible that intensive BP control exerts differential effects in patients with and without T2DM
- However, this argument seems counterintuitive given the strong relationship between high BP and CVD and the enhanced CVD risk of patients with T2DM. Indeed, the risk profile of adults with T2DM in the U.S. bears a striking similarity to that of SPRINT participants

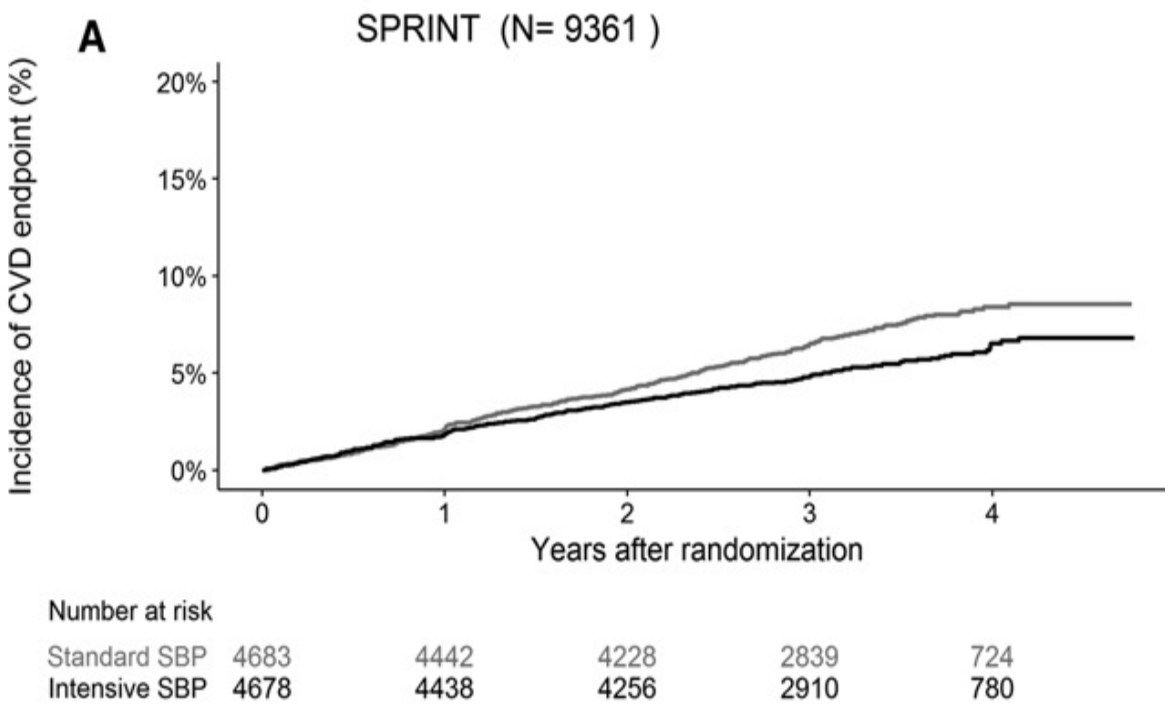
Why are ACCORD BP and SPRINT CV results different?

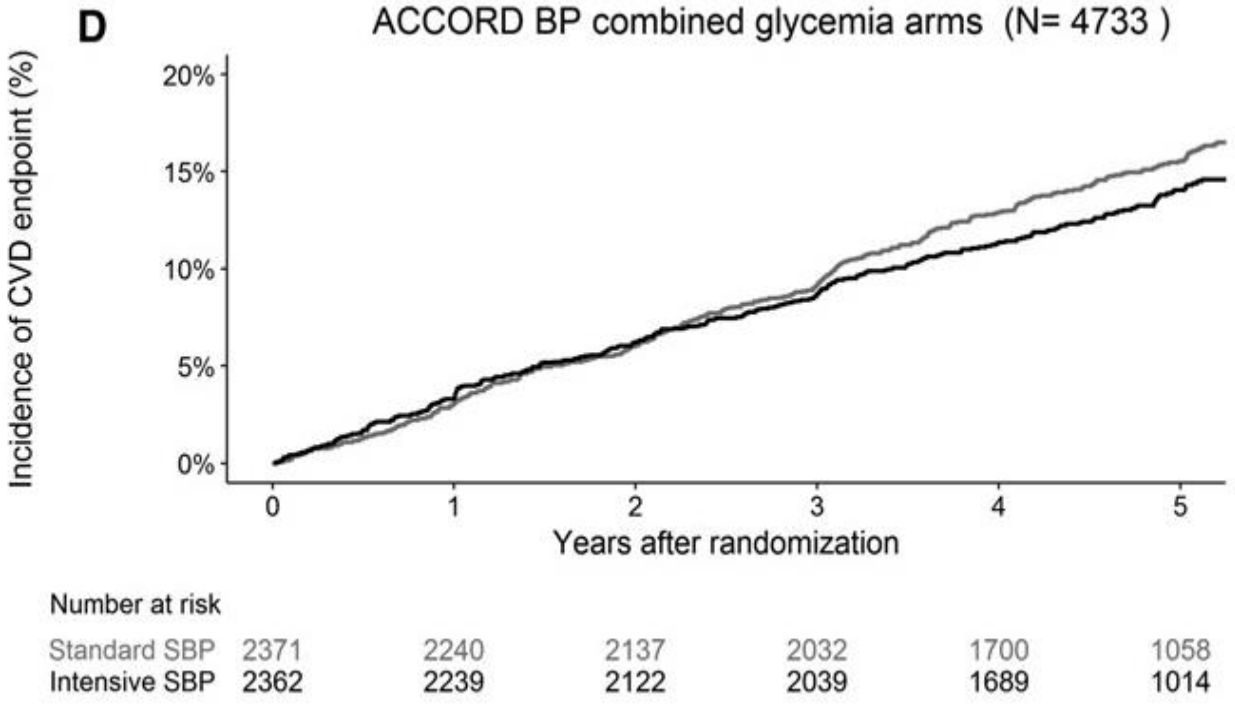


The often cited reason is that ACCORD BP had fewer participants than SPRINT and therefore, lower power.

Perkovic V, Rodgers A. N Engl J Med 373;2175-2178

ACCORD BP Had Higher Events Rate than SPRINT





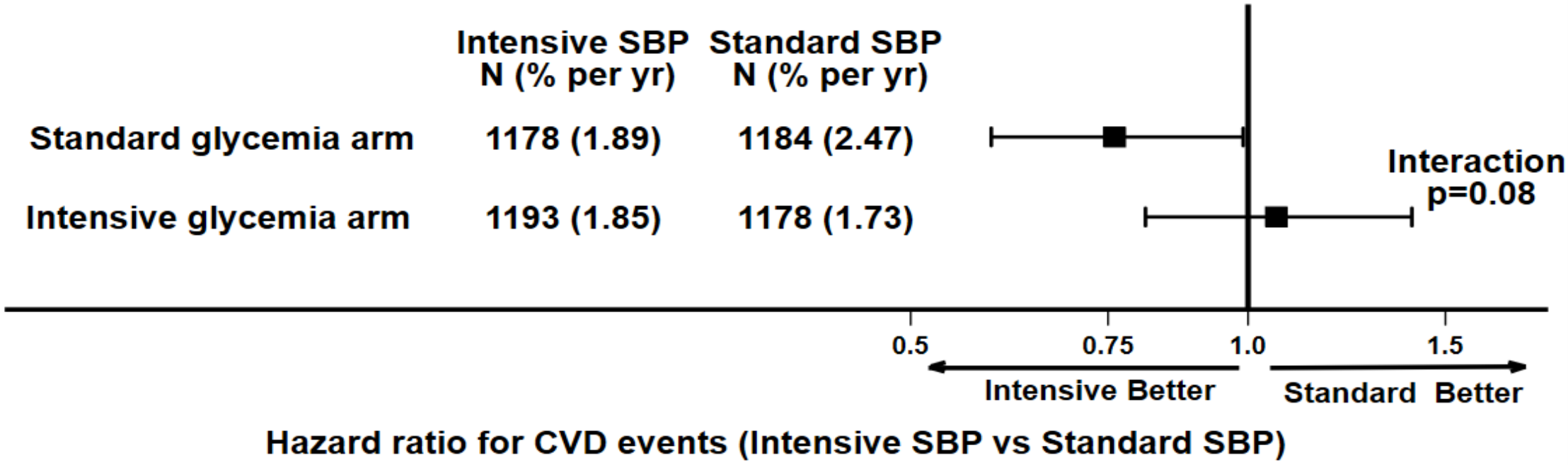
Beddhu S et al. J Am Heart Assoc. 2018;7:e009326. DOI: 10.1161/JAHA.118.009326

What about the Glycemia arm of ACCORD?

- The finding of higher mortality in the intensive-therapy group led to a discontinuation of intensive therapy after a mean of 3.5 years of follow-up
- 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard therapy group
  - Hazard ratio, 1.22; 95% CI, 1.01 to 1.46; P = 0.04
- The use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events.
- These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes mellitus.

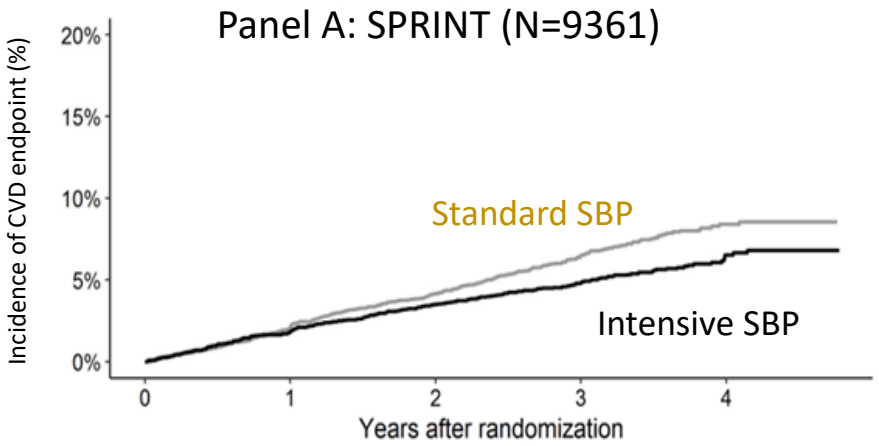
ACCORD study group. N Engl J Med 2008; 358:2545-59

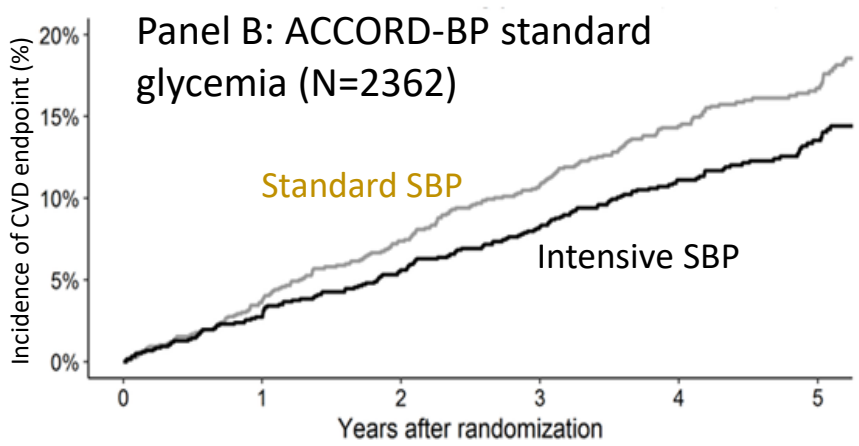
Potential interaction between intensive glycemia and intensive SBP arms for Primary CVD Outcome in ACCORD BP

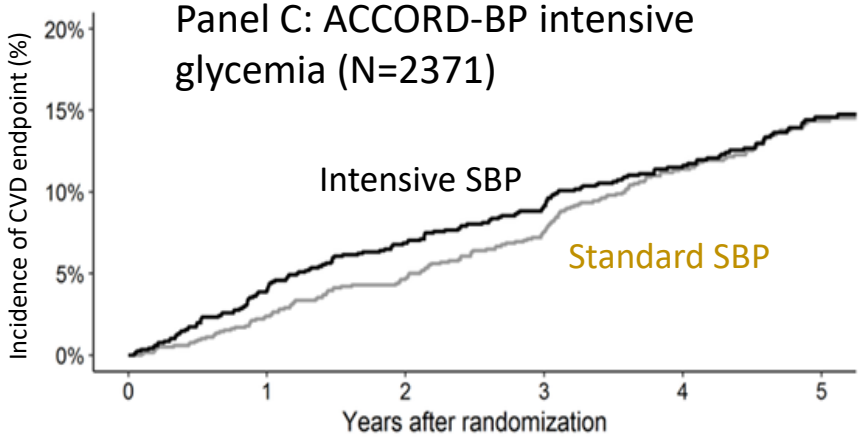


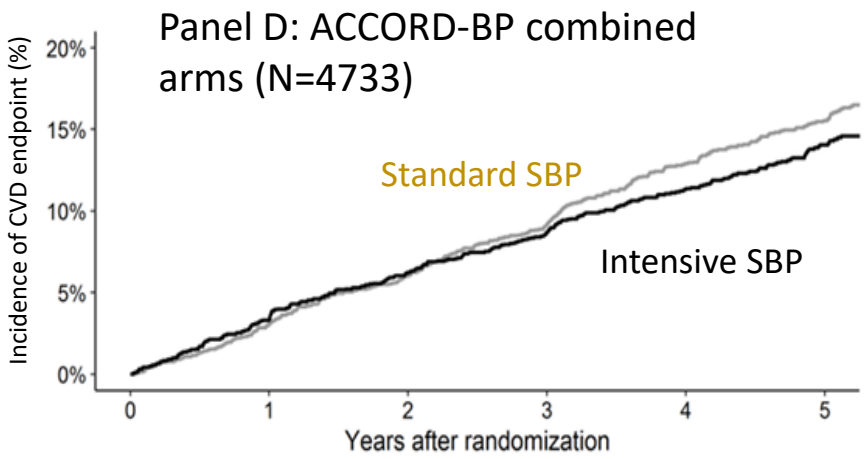
Supplement to: The ACCORD Study Group. N Engl J Med 2010; 362:1575-1585, Supplementary Appendix 1

CVD outcome: SPRINT vs ACCORD



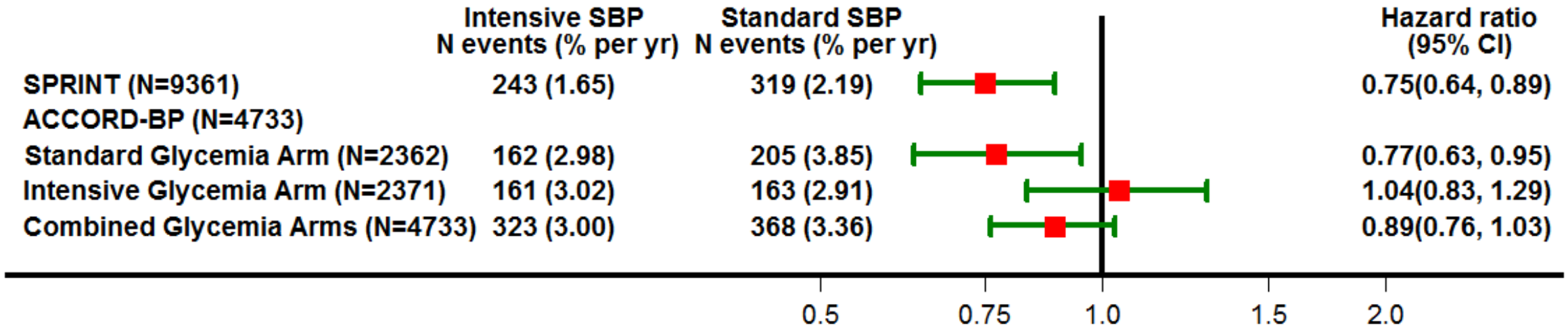






Beddhu S et al. J Am Heart Assoc. 2018;7:e009326. DOI: 10.1161/JAHA.118.009326

Forest Plot of HRs of Intensive vs. Standard SBP for CVD Outcome in SPRINT and Two Glycemic Arms in ACCORD BP

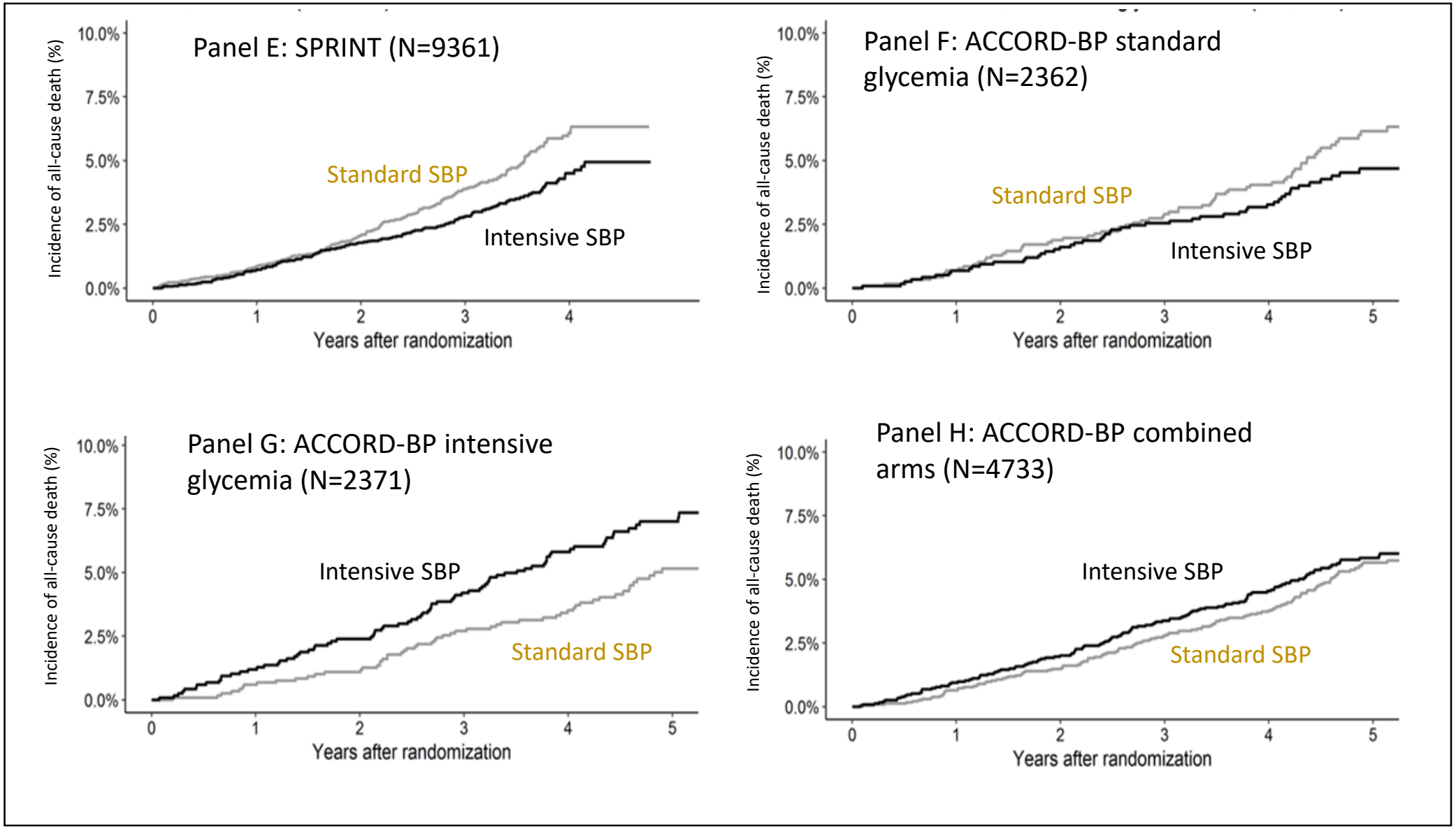


Interaction p-values for comparison of the effects of intensive SBP versus standard SBP

SPRINT vs. ACCORD-BP Standard Glycemia Arm	p=0.87	ACCORD-BP Intensive vs. standard Glycemia Arm	p=0.053
SPRINT vs. ACCORD-BP Intensive Glycemia Arm	p=0.023	SPRINT vs. ACCORD-BP Combined Glycemia Arms	p=0.16

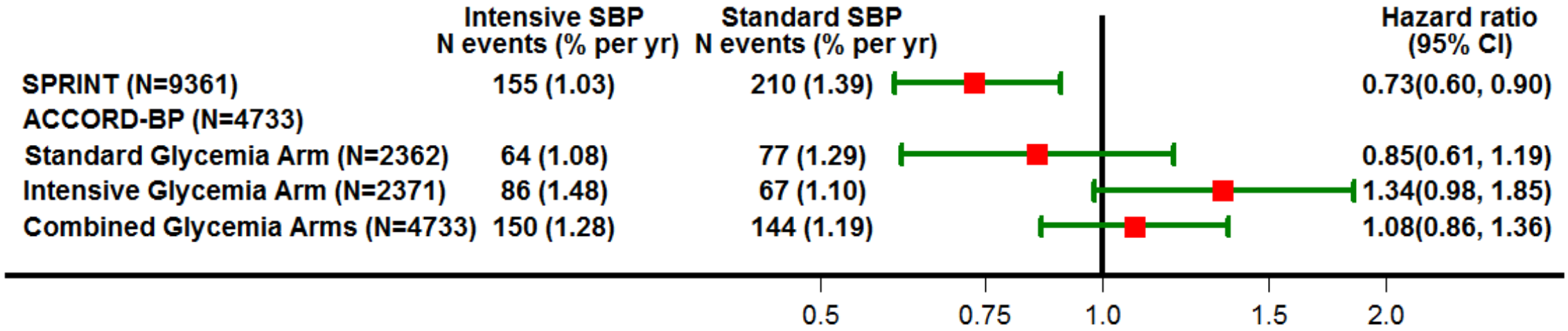
Beddhu S et al. J Am Heart Assoc. 2018;7:e009326. DOI: 10.1161/JAHA.118.009326

All-cause mortality: SPRINT vs ACCORD



Beddhu S et al. J Am Heart Assoc. 2018;7:e009326. DOI: 10.1161/JAHA.118.009326

Forest Plot of HRs of Intensive vs. Standard SBP for All-Cause Mortality Outcome in SPRINT and Two Glycemic Arms in ACCORD BP



Interaction p-values for comparison of the effects of intensive SBP versus standard SBP

SPRINT vs. ACCORD-BP Standard Glycemia Arm	p=0.46	ACCORD-BP Intensive vs. standard Glycemia Arm	p=0.051
SPRINT vs. ACCORD-BP Intensive Glycemia Arm	p=0.002	SPRINT vs. ACCORD-BP Combined Glycemia Arms	p=0.015

Beddhu S et al. J Am Heart Assoc. 2018;7:e009326. DOI: 10.1161/JAHA.118.009326

SPRINT vs ACCORD comparison

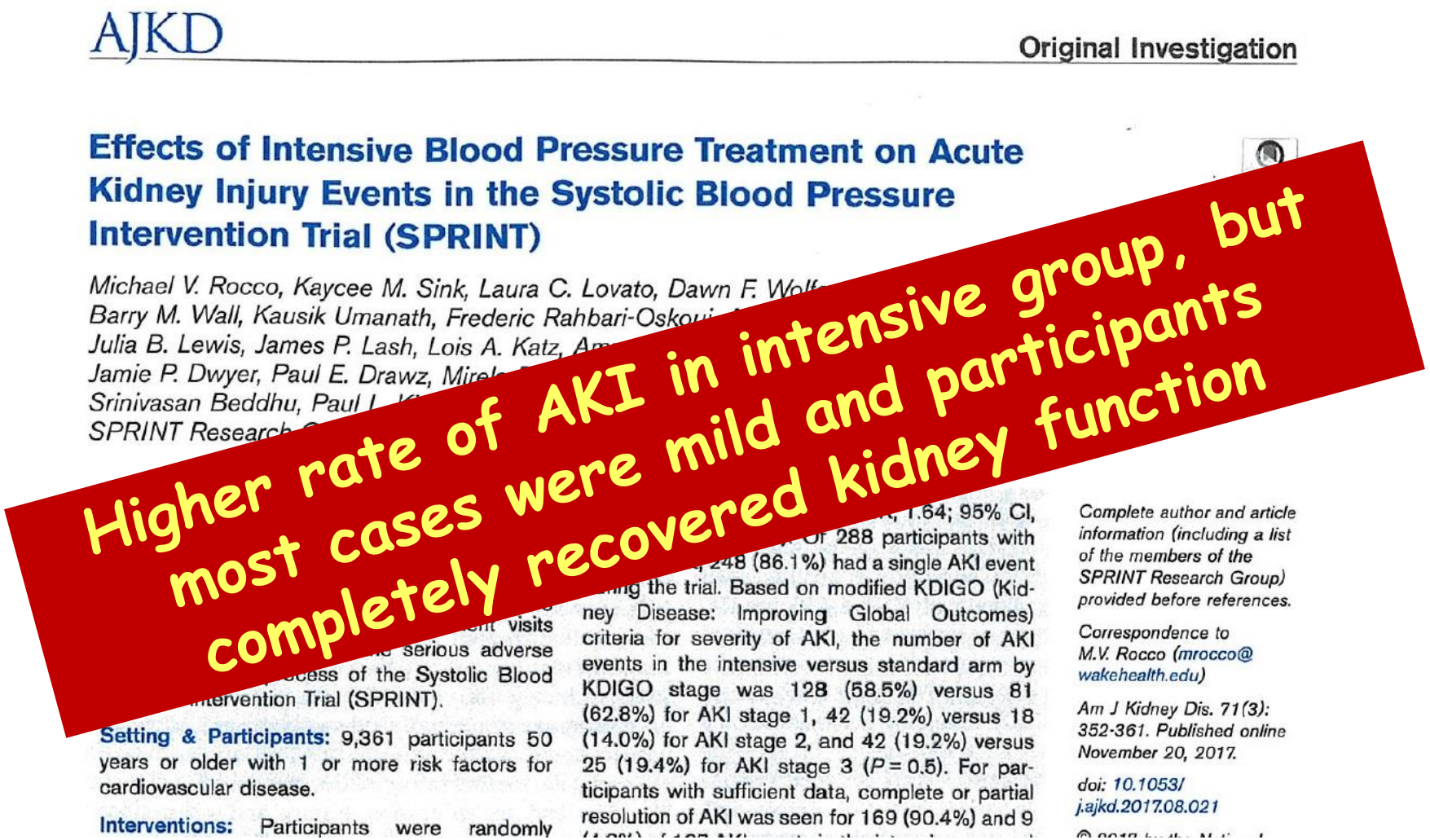
- Intensive SBP lowering decreased the hazard of the composite CVD end point similarly in SPRINT
  - Hazard ratio: 0.75; 95% confidence interval, 0.64 – 0.89)

  and in the ACCORD BP standard glycemia arm
  - Hazard ratio: 0.77; 95% confidence interval, 0.63 – 0.95; interaction P = 0.87
- Patterns were similar for all-cause mortality.

What Are the Clinical Implications?

- These findings support the current American College of Cardiology and American Heart Association guidelines of a systolic blood pressure goal of <130 mm Hg in patients both with and without type 2 diabetes mellitus.

Development of AKI in SPRINT



AJKD

Original Investigation

Effects of Intensive Blood Pressure Treatment on Acute Kidney Injury Events in the Systolic Blood Pressure Intervention Trial (SPRINT)

Michael V. Rocco, Kaycee M. Sink, Laura C. Lovato, Dawn F. Wolf
Barry M. Wall, Kausik Umanath, Frederic Rahbari-Oskoui
Julia B. Lewis, James P. Lash, Lois A. Katz, Am
Jamie P. Dwyer, Paul E. Drawz, Mirel
Srinivasan Beddhu, Paul L. Ki
SPRINT Research

visits
serious adverse
ocess of the Systolic Blood
ntervention Trial (SPRINT).

Setting & Participants: 9,361 participants 50 years or older with 1 or more risk factors for cardiovascular disease.

Interventions: Participants were randomly

.64; 95% CI,
Of 288 participants with
248 (86.1%) had a single AKI event
ng the trial. Based on modified KDIGO (Kidney Disease: Improving Global Outcomes) criteria for severity of AKI, the number of AKI events in the intensive versus standard arm by KDIGO stage was 128 (58.5%) versus 81 (62.8%) for AKI stage 1, 42 (19.2%) versus 18 (14.0%) for AKI stage 2, and 42 (19.2%) versus 25 (19.4%) for AKI stage 3 ($P = 0.5$). For participants with sufficient data, complete or partial resolution of AKI was seen for 169 (90.4%) and 9

Complete author and article information (including a list of the members of the SPRINT Research Group) provided before references.

Correspondence to M.V. Rocco (mrocco@wakehealth.edu)

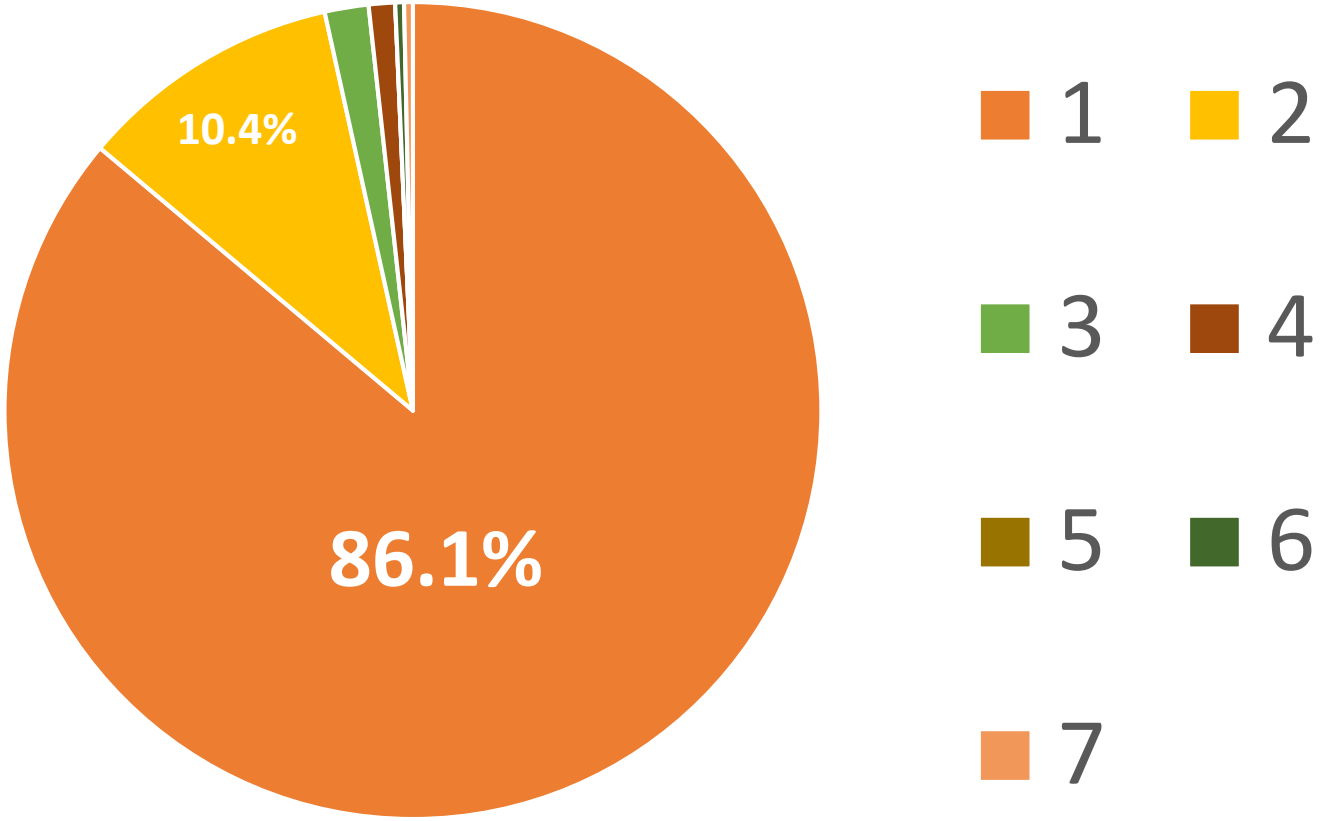
Am J Kidney Dis. 71(3): 352-361. Published online November 20, 2017.

doi: 10.1053/j.ajkd.2017.08.021

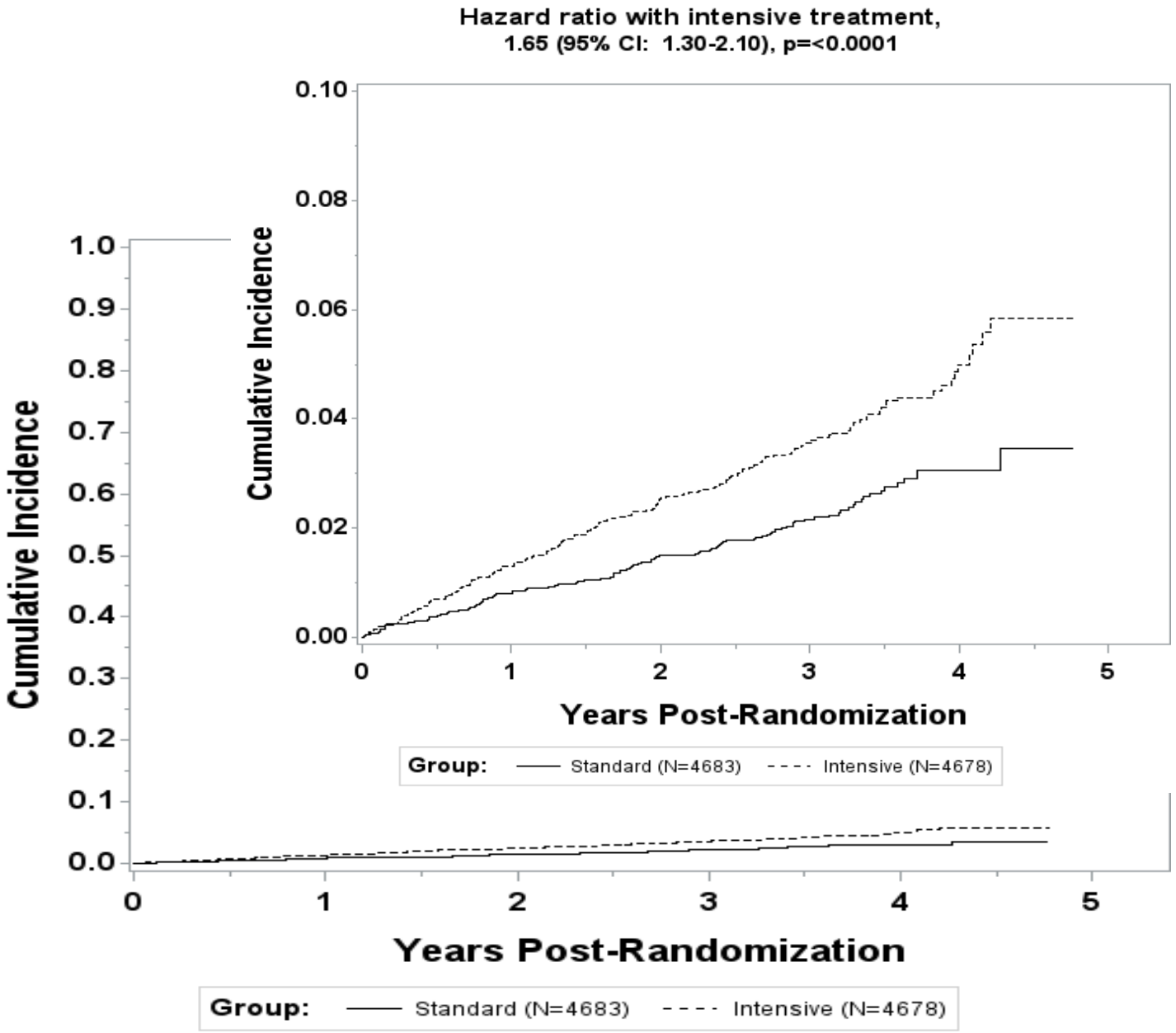
Higher rate of AKI in intensive group, but most cases were mild and participants completely recovered kidney function

Number of SPRINT adjudicated AKI events per participant

The vast majority of participants had only one AKI event during the trial



Rocco MV et al. Am J Kidney Dis 71: 352-361, 2018

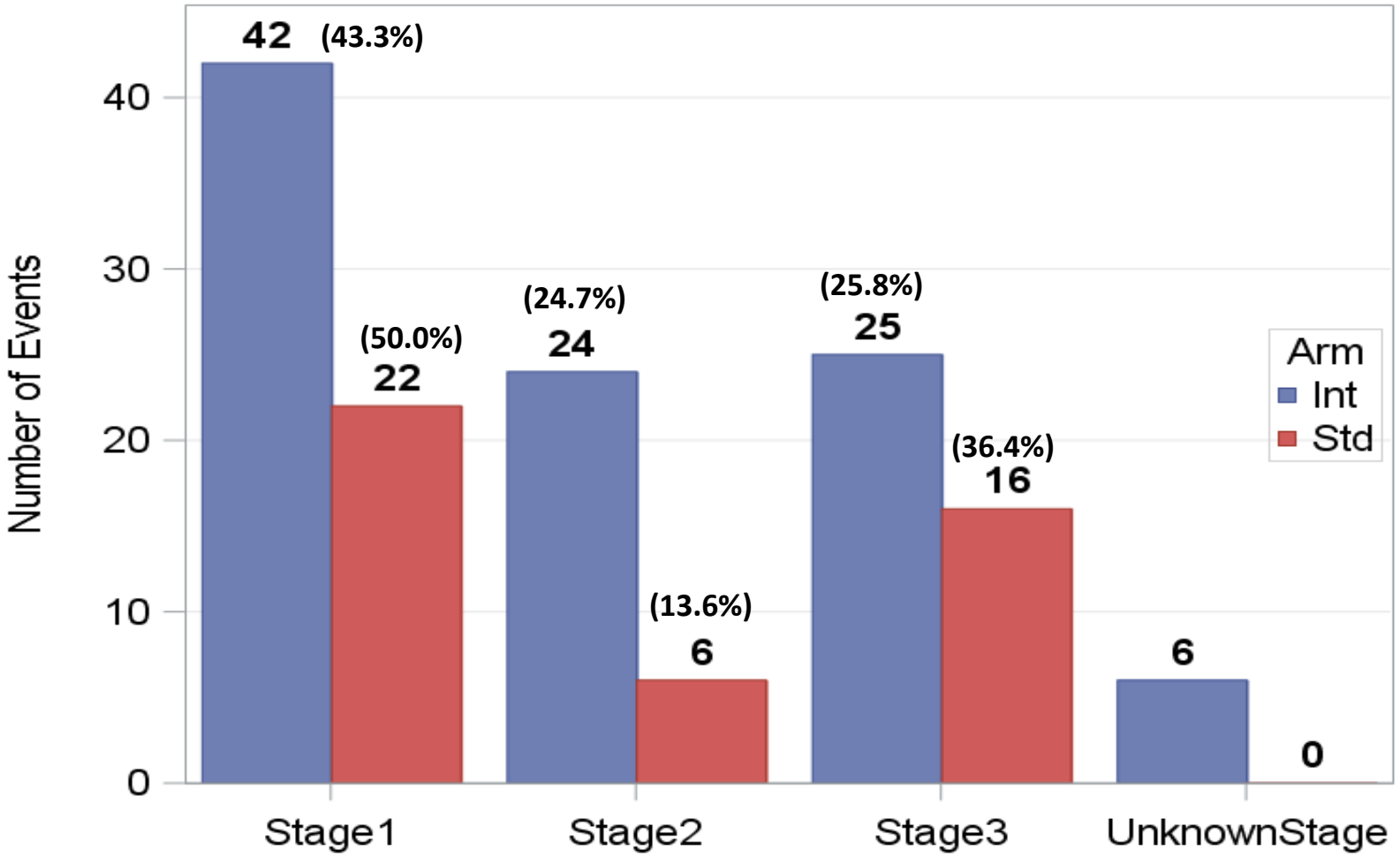


Hazard ratio for time to first AKI event with intensive treatment

Cox proportional hazards regression, with two-sided tests at the 5% level of significance, with stratification by clinical site. Follow-up time was censored at the time of the final event ascertainment.

Rocco MV et al. Am J Kidney Dis 71: 352-361, 2018

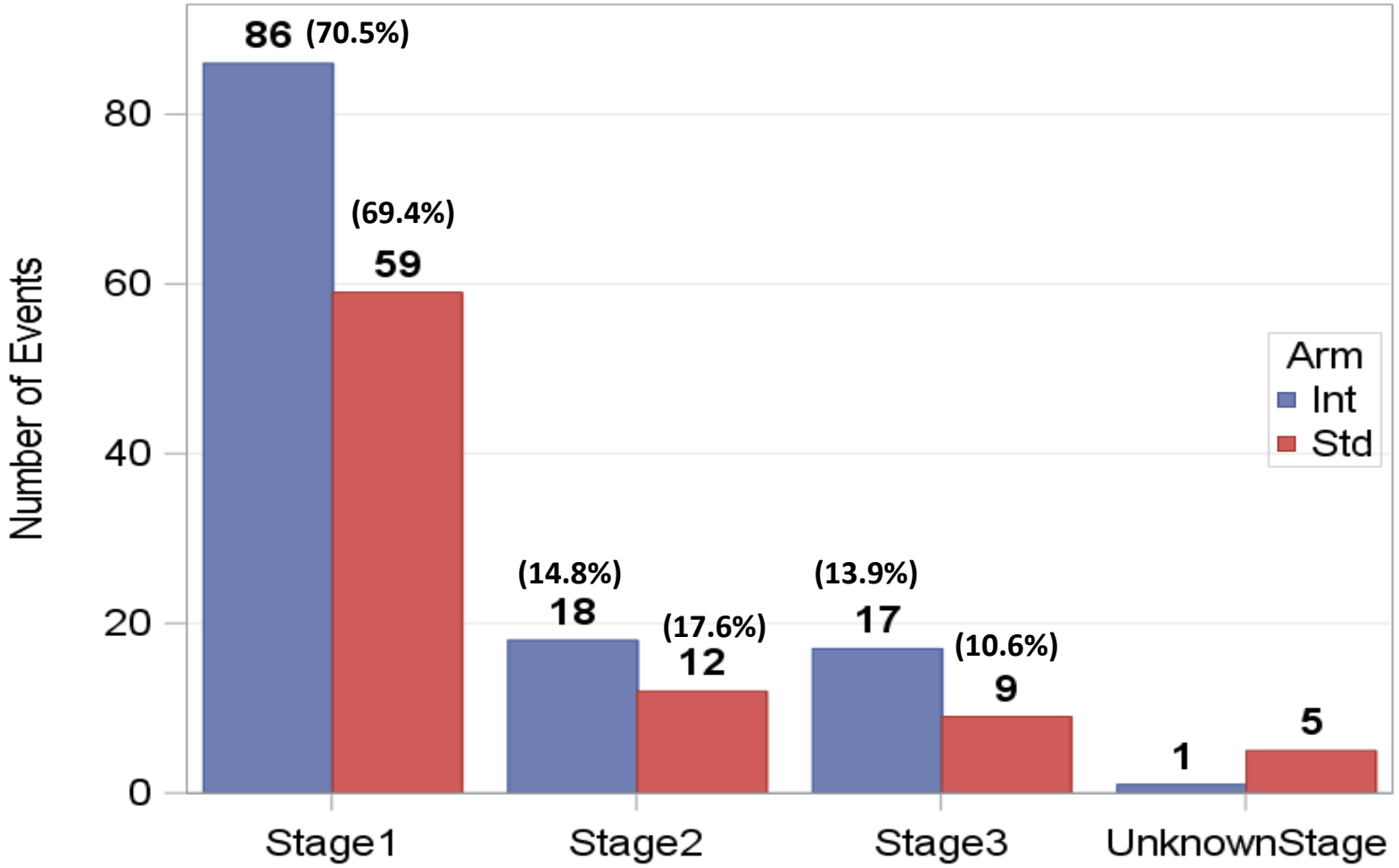
Similar severity of AKI in both arms of trial (Non-CKD cohort)



p-value = 0.20 for comparison of stages of AKI by randomized arm, excluding unknowns (All Events)

Rocco MV et al. Am J Kidney Dis 71: 352-361, 2018

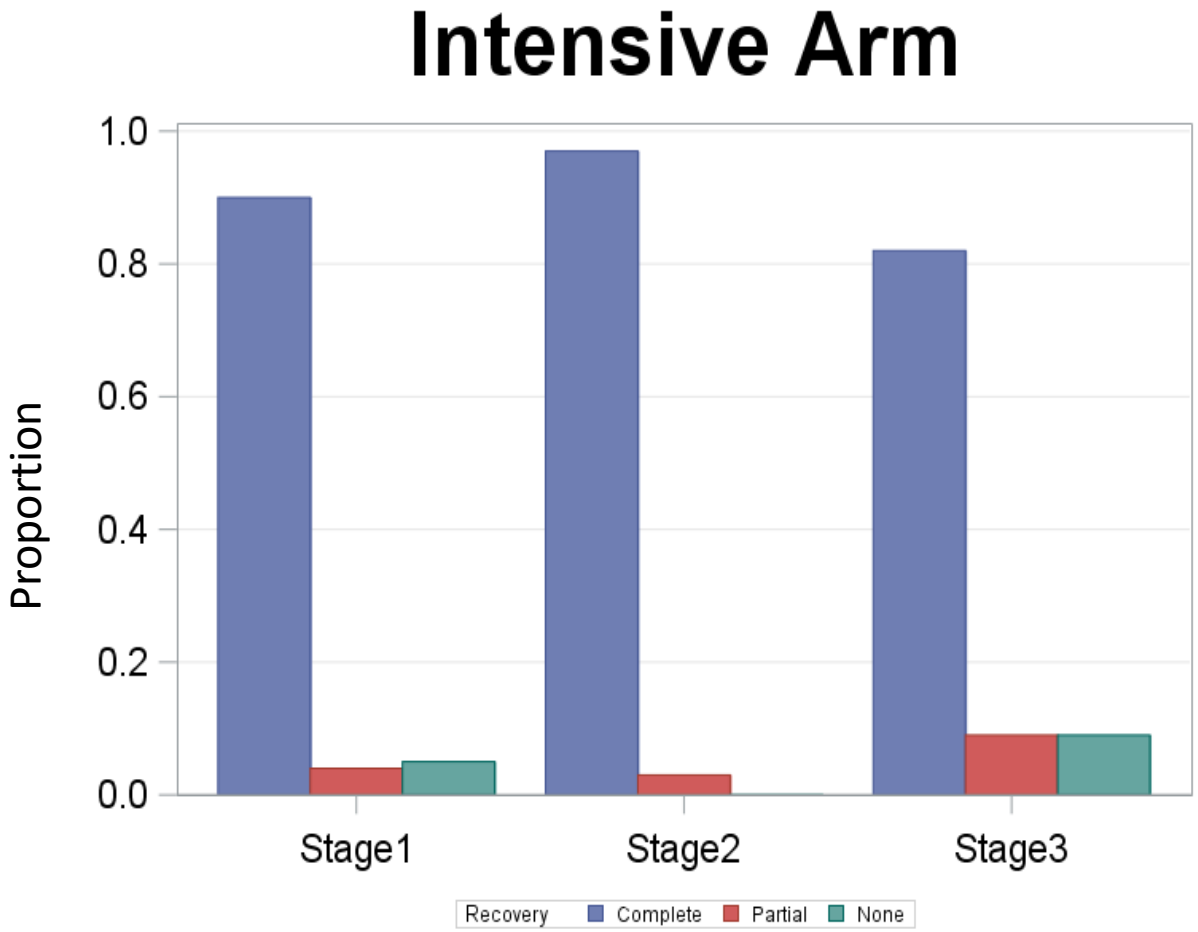
Similar severity of AKI in both arms of trial (CKD cohort)

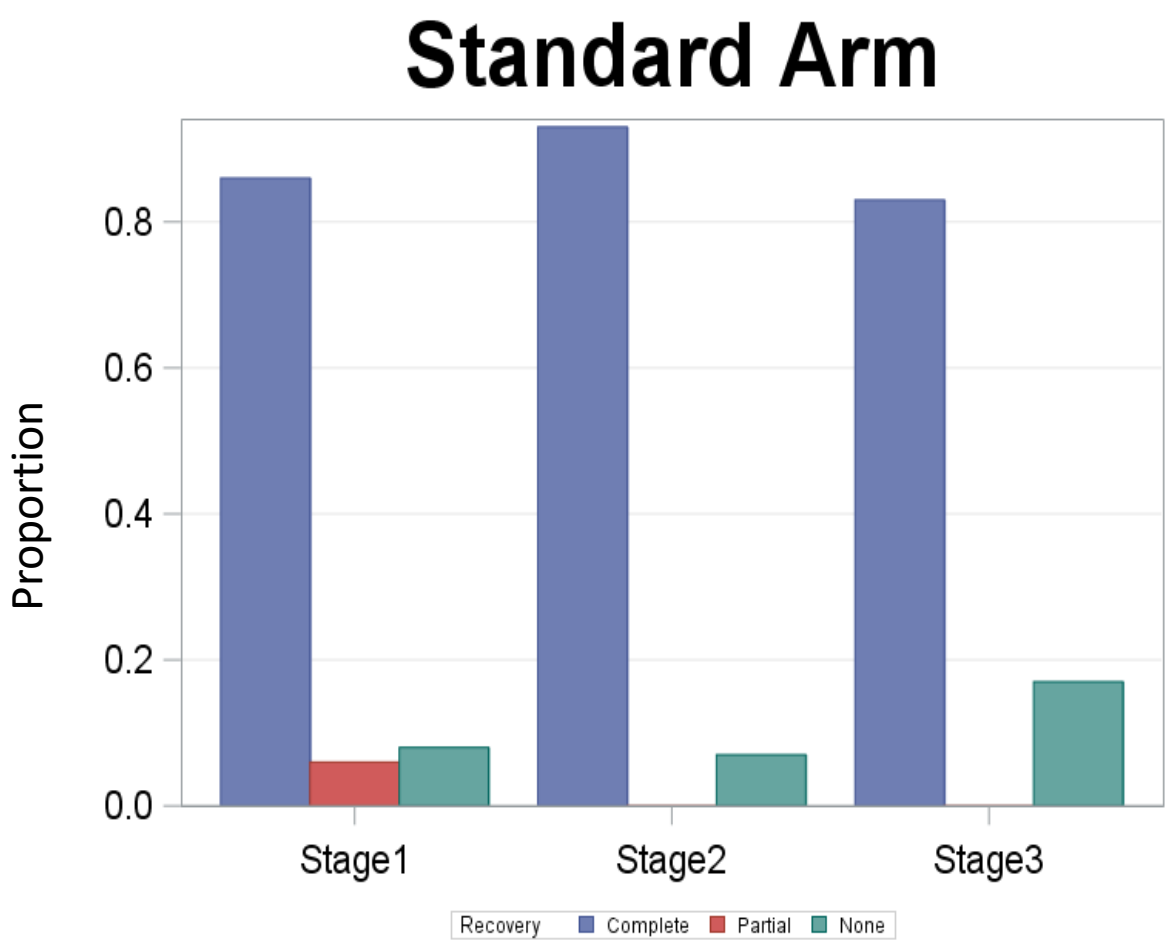


p-value = 0.84 for comparison of stages of AKI by randomized arm, excluding unknowns (All Events)

Rocco MV et al. Am J Kidney Dis 71: 352-361, 2018

Most participants recovered renal function after AKI event





Excludes 62 participants without follow-up, including 39 who were deceased prior to study endpoint

Recovery: Complete Partial None

Rocco MV et al. Am J Kidney Dis 71: 352-361, 2018

Summary

- Most participants had only one AKI event during the trial
- AKI events more common in intensive arm versus standard arm
  - Hazard ratio of 1.65, 95% confidence interval 1.30 – 2.10
- Most AKI events were KDIGO stage 1 (least severe)
- Similar severity of AKI events in intensive arm versus standard arm
- Complete recovery of AKI was seen in more than 90% of subjects
- Subjects with AKI were more likely to have experienced either the SPRINT primary outcome or death from any cause compared to subjects who did not have an AKI event

Rocco MV et al. Am J Kidney Dis 71: 352-361, 2018

Conclusions - 1

- Participants with CKD randomized to the intensive arm, compare to the standard arm had
  - Lower all-cause mortality
  - Trend towards fewer cardiovascular events
  - Tubular biomarker changes suggest that decrease in eGFR was a hemodynamic effect
- Participants greater than 75 years old randomized to the intensive arm compared to the standard arm had:
  - Lower all-cause mortality
  - Fewer cardiovascular events
  - No difference in gait speed
  - Lower rates of mild cognitive impairment
  - Smaller increase in white matter lesions
  - No difference in decrease in total brain volume

Conclusions - 2

- Post-hoc analysis of the ACCORD data demonstrates that
  - Those participants in the standard glycemic arm had similar rates of CV events and all cause mortality as found in the SPRINT study
    - Intensive therapy CV outcomes: 0.77 (95% CI 0.63 – 0.95) for ACCORD;
      0.75 (95% CI: 0.64 - 0.89) for SPRINT
    - Intensive therapy all cause mortality: 0.85 (95% CI: 0.61 – 1.19) for ACCORD
      0.73 (95% CI: 0.60 – 0.90) for SPRINT
- Acute Kidney injury events
  - Majority of events were mild in nature (KDIGO stage 1)
  - More than 80% of participants in both arms of the study recovered renal function to within 20% of pre-AKI values.

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)

Studies Comparing Unattended vs Attended Office Blood Pressure Measurements Taken Using Automated Devices

Study	No. of Subjects	Subjects; Visits	BP Measurements; Device Type	Average Attended BP Levels (mm Hg)	Unattended vs Attended BP Difference (mm Hg)
Stergiou et al[7] (2003)	n=30, attended and unattended	Same subjects; separate visits	3 measurements; Omron HEM-705CP	S: 139.6±16.0	S: −1.9 (−4.2 to 0.4)
				D: 88.6±8.1	D: −1.6 (−3.3 to 0.2)
Greiver et al[8] (2012)	n=50, attended (open areas) and unattended	Same subjects; same visit	6 measurements (first discarded); BpTRU	S: 121.1±17.9	S: −1.8 (−3.6 to 0.1)
				D: 73.9±10.2	D: −0.8 (−2.5 to 0.8)
Al-Karkhi et al[9] (2015)	n=162, attended and unattended	Same subjects; same visit	3 measurements; Omron i-C10	S: 139.1±18.0	S: −1.1 (−2.5 to 0.3)
				D: 84.8±11.0	D: 1.1 (−0.1 to 2.3)
Rinfret et al[10] (2017)	n=65, attended (open areas) and unattended	Same subjects; same visit	6 measurements (first discarded); BpTRU	S: 126.7±16.1	S: 0.2 (−1.6 to 2.0)
				D: 73.4±8.1	D: −0.7 (−1.6 to 0.2)
Bauer et al[11] (2018)	n=51, attended and unattended	Same subjects; same visit	3 measurements; Omron HEM-907	S: 135.7±21.5	S: −1.5 (−1.1 to 0.9)
				D: 80.6±12.0	D: 0.0 (−0.7 to 0.7)
Johnson et al[3] (SPRINT; 2018)	Intensive arm: attended n=1123; unattended n=2037	Different subjects	3 measurements; Omron HEM-907	S: 139.2±15.8	Intensive arm: S: 0.4 (−0.8 to 1.6)
				D: 79.3±12.1	D: −1.4 (−2.3 to −0.5)
	Standard arm: attended n=1124; unattended n=2045			S: 138.8±15.3	Standard arm: S: 1.1 (−0.0 to 2.2)
				D: 78.7±11.6	D: −0.7 (−1.6 to 0.2)

Mean±SD (95% CIs). BP indicates blood pressure; D, diastolic BP; and S, systolic BP.

Stergiou G et al. *Hypertension*. 2018;71:813-815