Main Outcomes of the Systolic Blood Pressure Intervention Trial (SPRINT) in Patients Age 75 and Older

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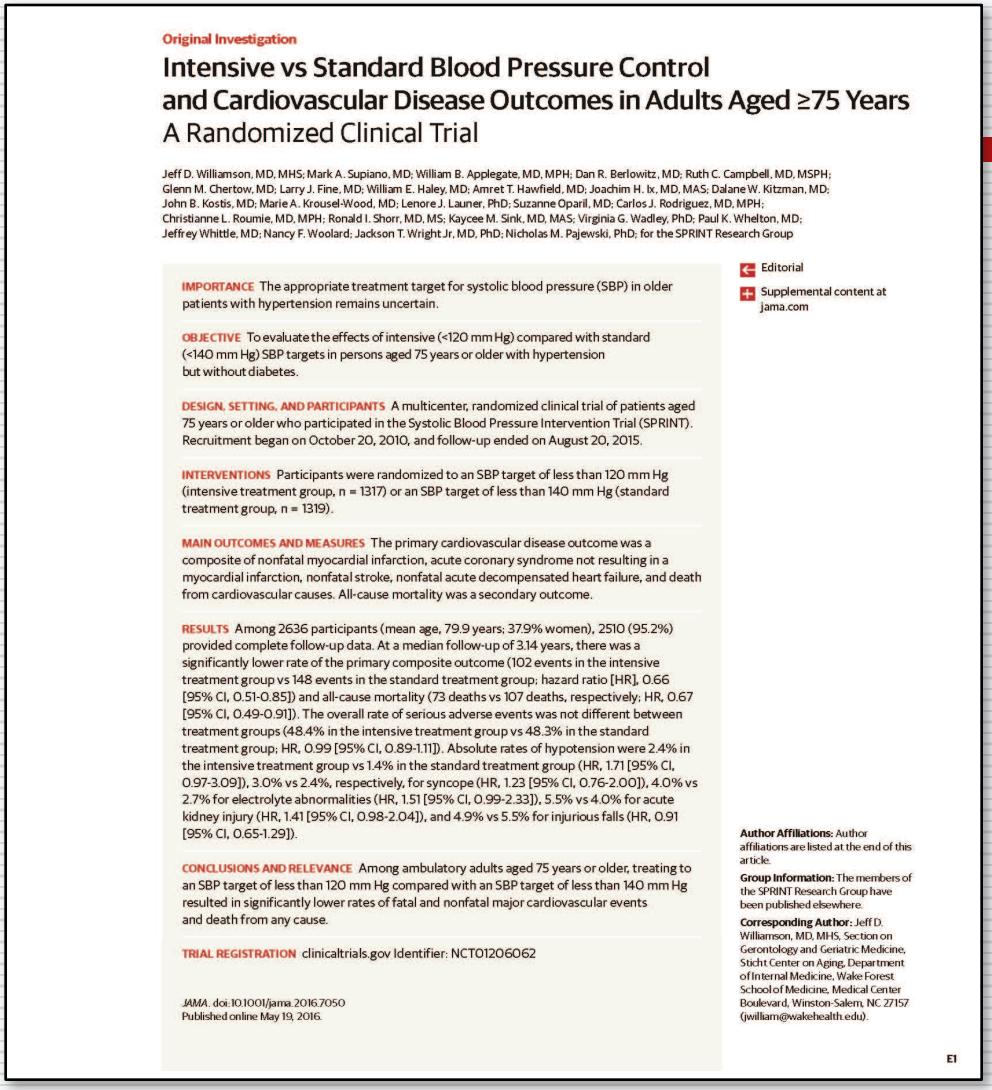

Original Investigation

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

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IMPORTANCE The appropriate treatment target for systolic blood pressure (SBP) in older patients with hypertension remains uncertain.

OBJECTIVE To evaluate the effects of intensive (<120 mm Hg) compared with standard (<140 mm Hg) SBP targets in persons aged 75 years or older with hypertension but without diabetes.

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 (intensive treatment group, n = 1317) or an SBP target of less than 140 mm Hg (standard treatment group, n = 1319).

MAIN OUTCOMES AND MEASURES The primary cardiovascular disease outcome was a composite of nonfatal myocardial infarction, acute coronary syndrome not resulting in a myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular causes. All-cause mortality was a secondary outcome.

RESULTS Among 2636 participants (mean age, 79.9 years; 37.9% women), 2510 (95.2%) provided complete follow-up data. At a median follow-up of 3.14 years, there was a significantly lower rate of the primary composite outcome (102 events in the intensive treatment group vs 148 events in the standard treatment group; hazard ratio [HR], 0.66 [95% CI, 0.51-0.85]) and all-cause mortality (73 deaths vs 107 deaths, respectively; 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]). Absolute rates of hypotension were 2.4% in the intensive treatment group vs 1.4% in the standard treatment group (HR, 1.71 [95% CI, 0.97-3.09]), 3.0% vs 2.4%, respectively, for syncope (HR, 1.23 [95% CI, 0.76-2.00]), 4.0% vs 2.7% for electrolyte abnormalities (HR, 1.51 [95% CI, 0.99-2.33]), 5.5% vs 4.0% for acute kidney injury (HR, 1.41 [95% CI, 0.98-2.04]), and 4.9% vs 5.5% for injurious falls (HR, 0.91 [95% CI, 0.65-1.29]).

CONCLUSIONS AND RELEVANCE Among ambulatory adults aged 75 years or older, treating to an SBP target of less than 120 mm Hg compared with an SBP target of less than 140 mm Hg resulted in significantly lower rates of fatal and nonfatal major cardiovascular events and death from any cause.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01206062

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Editorial

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the SPRINT Research Group have been published elsewhere.

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JD Williamson and Coauthors for the SPRINT Research Group

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

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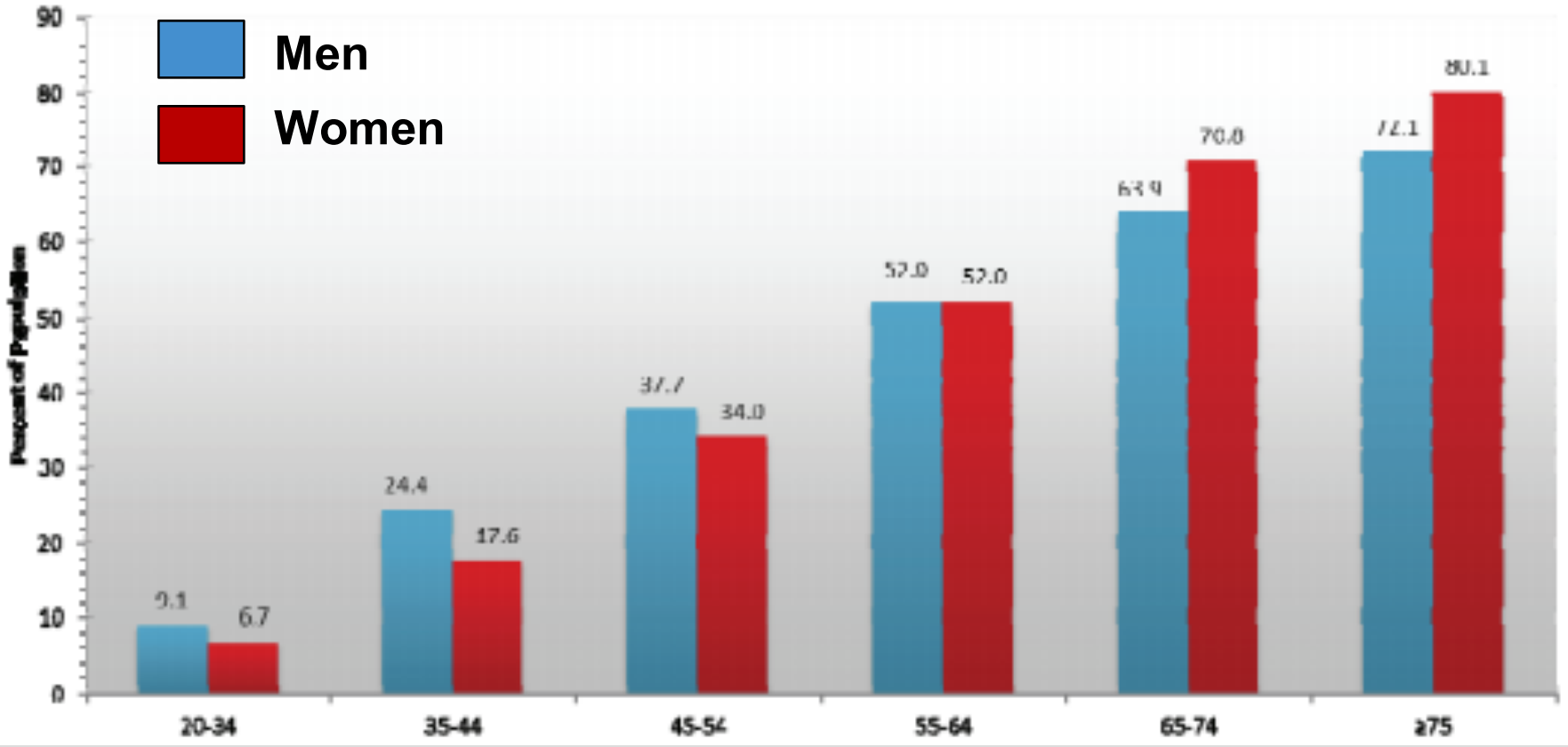
The JAMA Network

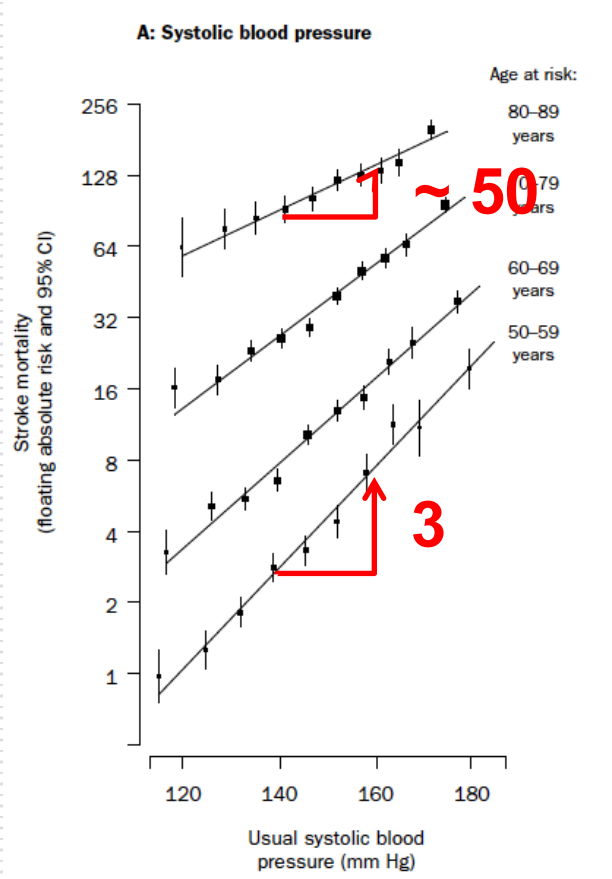
Outline

1. Background – How low should we go?
2. SPRINT-Senior
   a) Design and geriatric outcome measures: Frailty status and gait speed
   b) Baseline characteristics
   c) Results by frailty status and gait speed
   d) Adverse events including injurious falls
3. Summary and Conclusions

Prevalence of Hypertension: Age and Sex



SBP vs stroke mortality risk relationship



- No apparent threshold
- Stroke mortality risk doubles for every 20/10 mm Hg increase above 115/75
- 20 mm Hg increase associated with a 10-fold larger annual absolute stroke risk in 80s vs. 50s.

Lewington Lancet 2002

Healthy age 60 to 80: What SBP Target?

1. < 120 mm Hg
2. < 140 mm Hg
3. < 150 mm Hg
4. < 160 mm Hg
5. < (100 + age) mm Hg

How low should we go?

- “The panel agreed that more research is needed to identify optimal goals of SBP…” JNC 8
- Equipoise
- Systolic Blood Pressure Intervention Trial (SPRINT) launched in 2010

Background – SPRINT Senior

- Optimal SBP target especially controversial in older, frail patients
  - Epidemiological evidence of inverse relationship between SBP and mortality
  - Concerns regarding falls and fall-related injury due to antihypertensive therapy
  - Cognitive and quality of life outcomes not certain
- ARRA-funded initiative within SPRINT to enhance the number of persons aged 75+ enrolled in the trial
- Ambulatory, community-dwelling older adults
- No nursing home or assisted living facility residents or prevalent dementia enrolled (at baseline)

Major Exclusion Criteria

- Stroke (SPS3)
- Diabetes mellitus (ACCORD)
- Congestive heart failure (symptoms or EF < 35%)
- CKD with eGFR < 20 mL/min/1.73m^2 (MDRD
- Standing BP < 110 mm Hg

BP Measurement in SPRINT: Automated Office BP (AOBP)

- Visit BP was the average of 3 seated office BP measurements obtained using an automated measurement device: Omron 907XL.
- Appropriate cuff size was determined by arm circumference.
- Participant was seated with back supported and arm bared and supported at heart level.
- Device was set to delay 5 minutes to begin 3 BP measurements – research staff was trained to push start button and leave exam room during the 5 minute delay and measurements, during which time participant refrained from talking.

Geriatric Outcome Measures

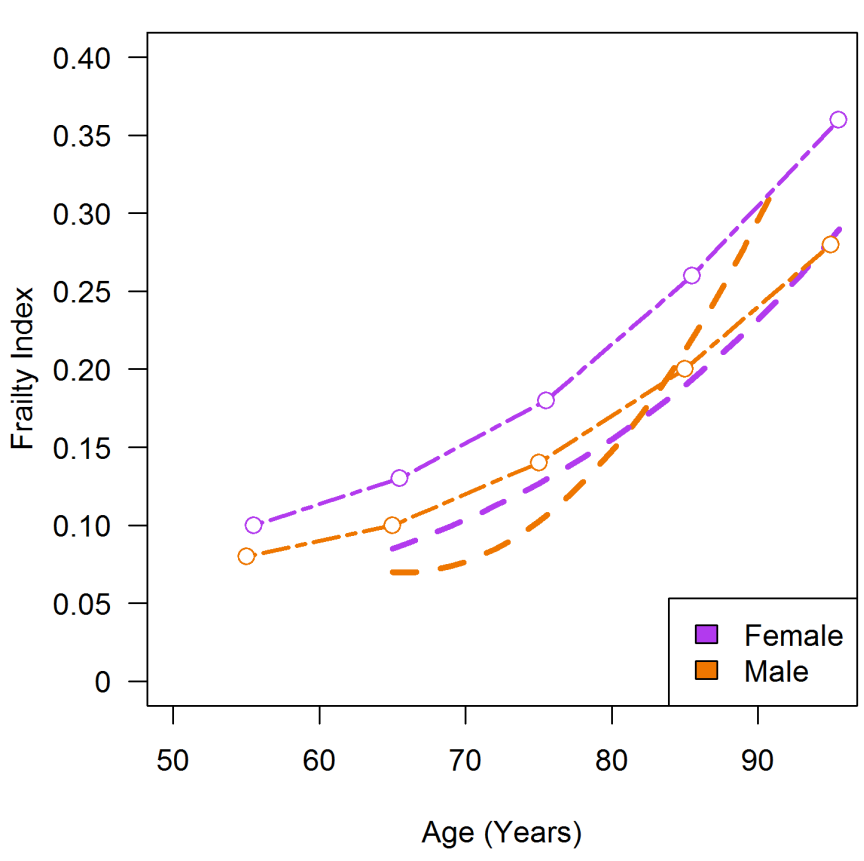
- Assessments
  - Gait speed – 4 m walk
- Frailty status
- Cognitive battery and brain MRI – SPRINT-MIND
- Adverse Events
  - PHQ-9 and Health Related Quality of Life
  - Falls and injurious falls
  - Orthostatic hypotension +/- dizziness
  - Hospitalizations and Nursing home placement

Frailty Index

- Deficit accumulation approach
- Assess a large number of aging-related deficits, usually at least 30 deficits
- Scores range from 0 to 1 – higher values denote more deficits
- Values > 0.7 not observed

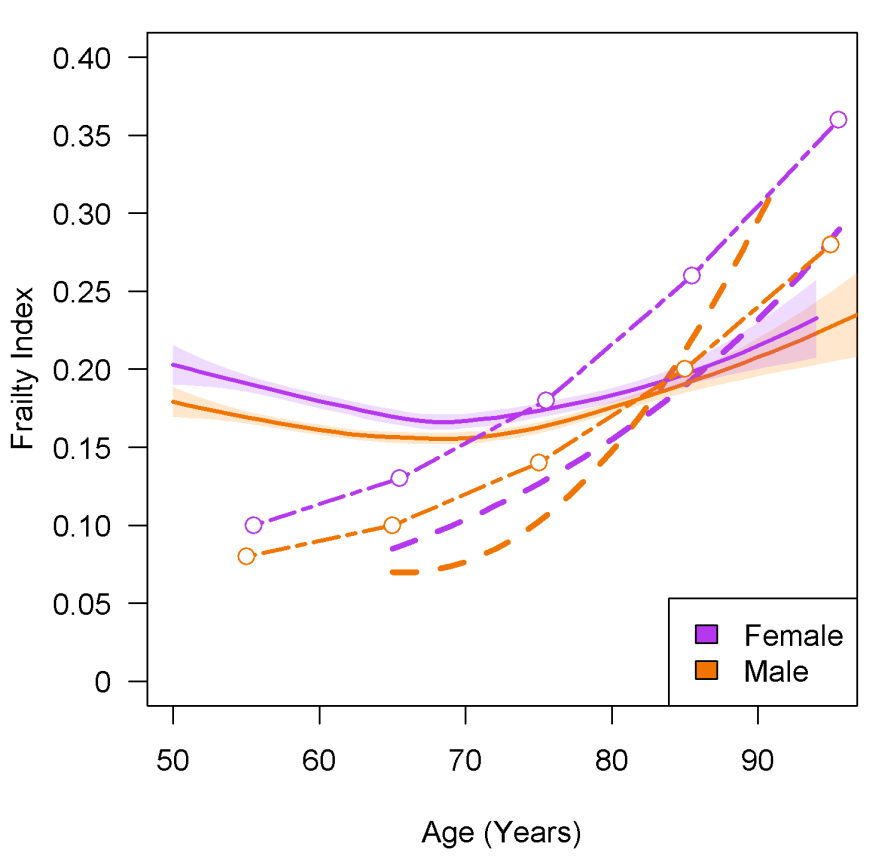
Clegg et al. *Lancet* 2013;381:752-62; Searle et al. *BMC Geriatrics* 2008;8(24); Walston and Bandeen-Roche. *BMC Medicine* 2015;13(185)

Relationship of FI with Age



- Single dash lines: Estimates from National Long Term Care Survey Kulminski *et al. Mech Ageing Dev* 2006;127:840-8
- Double dash lines: 10-year mean FI values from Survey of Health, Ageing and Retirement in Europe (SHARE) Romero-Ortuno and Kenny. *Age Ageing* 2012;41(5):684-9

Relationship of SPRINT Cohort FI with Age



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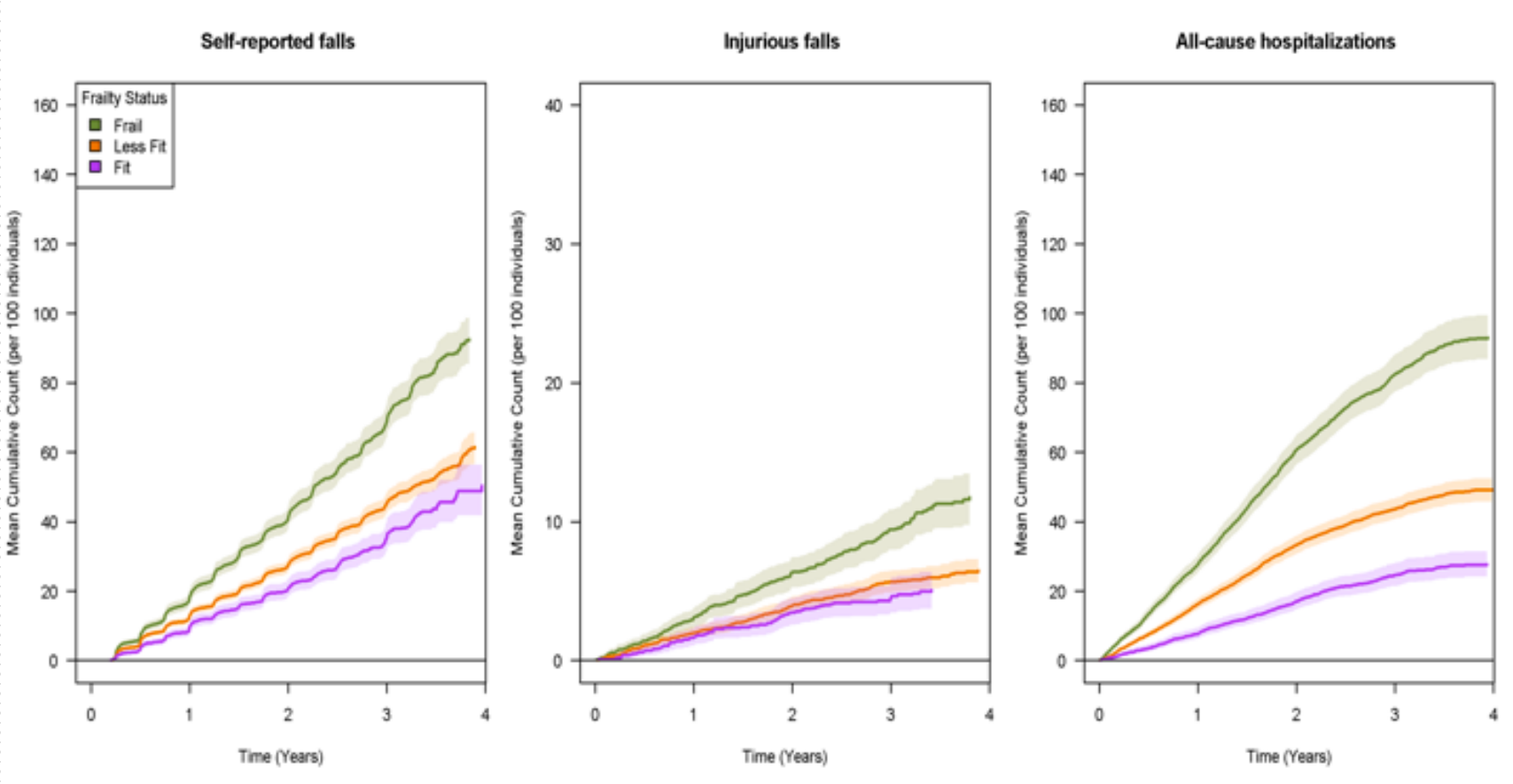
- Double dash lines: 10-year mean FI values from Survey of Health, Ageing and Retirement in Europe (SHARE) Romero-Ortuno and Kenny. *Age Ageing* 2012;41(5):684-9
- Solid lines: Fit based on local polynomial regression in SPRINT with 95% CIs (shaded areas)

Pajewski, et al J Geron. 2016

Adverse Events by Frailty Status



Pajewski, et al J Geron. 2016

Baseline Characteristics: Participants 75 years or older

	Intensive N=1,317	Standard N=1,319	p-value
Age (years)	79.8 ± 3.9	79.9 ± 4.1	0.405
Gender (female)	499 (37.9)	501 (38)	0.992
Race/Ethnicity			0.879
White	977 (74.2)	987 (74.8)	
Black	225 (17.1)	226 (17.1)	
Hispanic	89 (6.8)	85 (6.4)	
Other	26 (2)	21 (1.6)	
History of CVD	338 (25.7)	309 (23.4)	0.197
10-year Framingham risk (%)	24.2 (16.8-32.8)	25 (17-33.4)	0.475
Number of antihypertensive meds	1.9 ± 1	1.9 ± 1	0.173
Baseline blood pressure (mmHg)			
Systolic	141.6 ± 15.7	141.6 ± 15.8	0.986
Diastolic	71.5 ± 11	70.9 ± 11	0.177
Body Mass Index (kg/m^2)	27.8 ± 4.9	27.7 ± 4.6	0.464
eGFR (CKD-EPI, ml/min/1.73m^2)	61.4 ± 17	61.2 ± 16.7	0.764
eGFR<60 ml/min/1.73m^2	614 (46.9)	608 (46.4)	0.859
Urine albumin / creatinine (mg/g)	13 (7.2-31.6)	13.4 (7.2-33.4)	0.505
Total cholesterol (mg/dL)	181.4 ± 39	181.8 ± 38.7	0.767
Fasting plasma glucose (mg/dL)	97.9 ± 12.1	98.2 ± 11.6	0.606

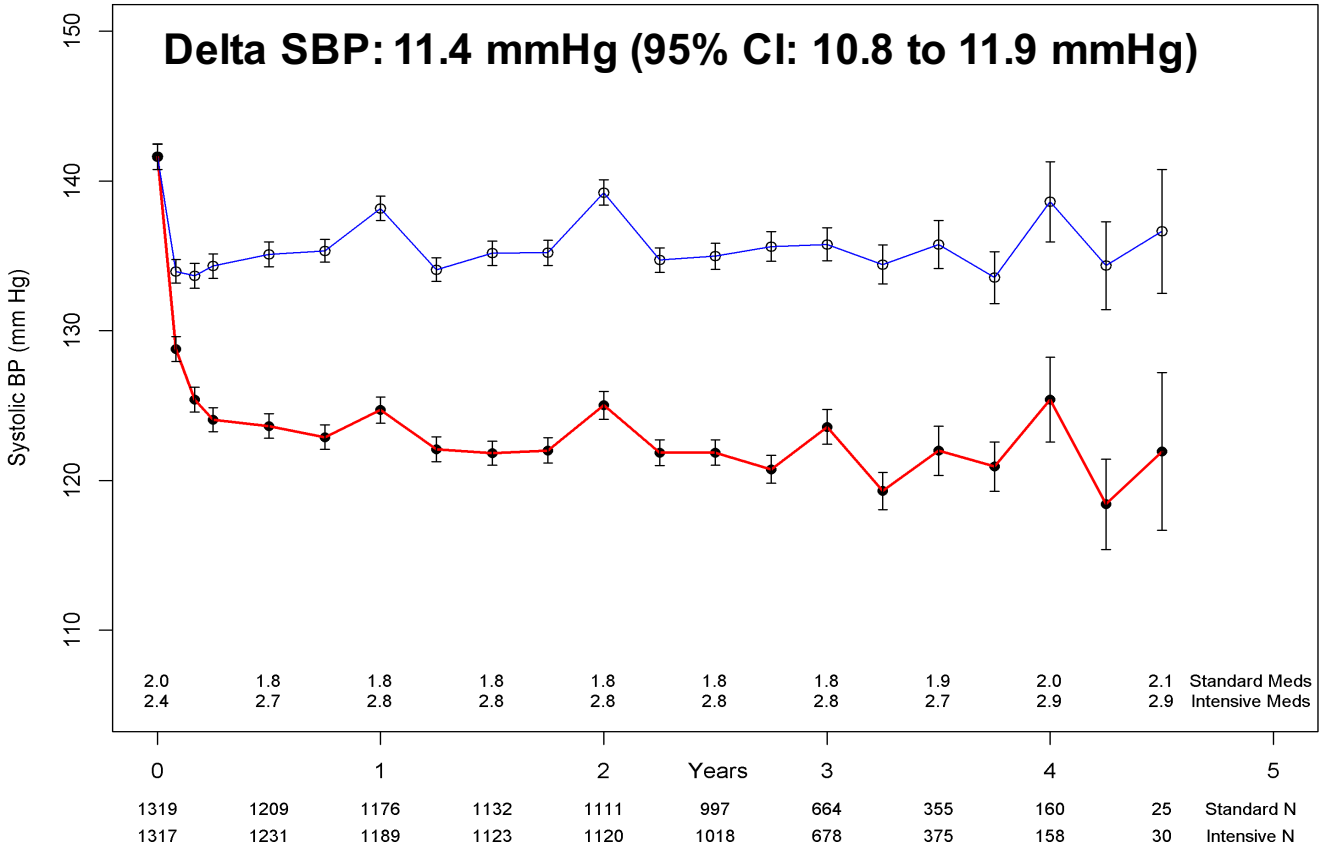
Values are N (%), mean ± SD, or median (IQR)

Baseline Characteristics: Participants 75 years or older

	Intensive N=1,317	Standard N=1,319	p-value
Gait speed (m/s)	0.90 (0.77-1.05)	0.92 (0.77-1.06)	0.375
Gait speed <0.8 m/s	371 (29.7)	369 (29.2)	0.853
Frailty Index	0.18 (0.13-0.23)	0.17 (0.12-0.22)	0.004
Frailty Status			0.013
Fit (FI≤0.10)	159 (12.1)	190 (14.5)	
Less fit (0.10<FI≤0.21)	711 (54.3)	745 (56.9)	
Frail (FI>0.21)	440 (33.6)	375 (28.6)	
MoCA score (0 to 30)	22 (19-25)	22 (19-25)	0.701
VR-12 Physical Component Summary Score	43.8 ± 10.2	44.3 ± 9.8	0.242
VR-12 Mental Component Summary Score	54.8 ± 8.5	55.3 ± 8.2	0.135

(MoCA) Montreal Cognitive Assessment
(VR-12) Veteran's RAND 12-item Health Survey
Values are N (%), mean ± SD, or median (IQR)

Systolic BP During Follow-up



Standard-treatment
134.8 mmHg
95% CI (134.3, 135.)

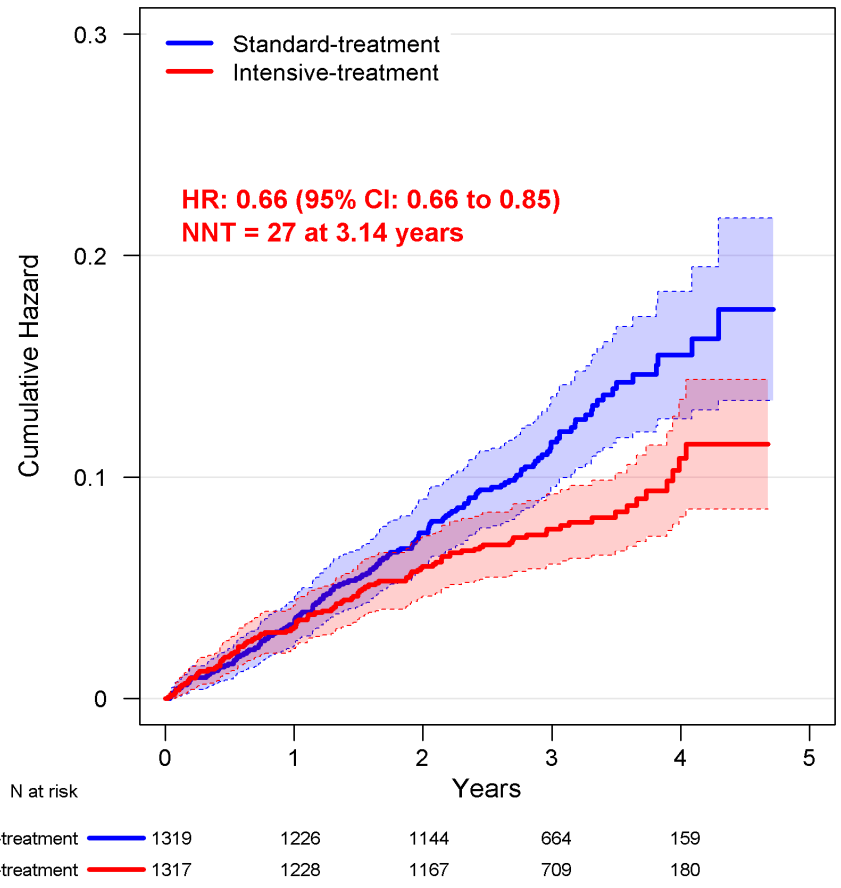
Intensive-treatment
123.4 mmHg
95% CI (123.0, 123.9)

# of classes of antihypertensive meds

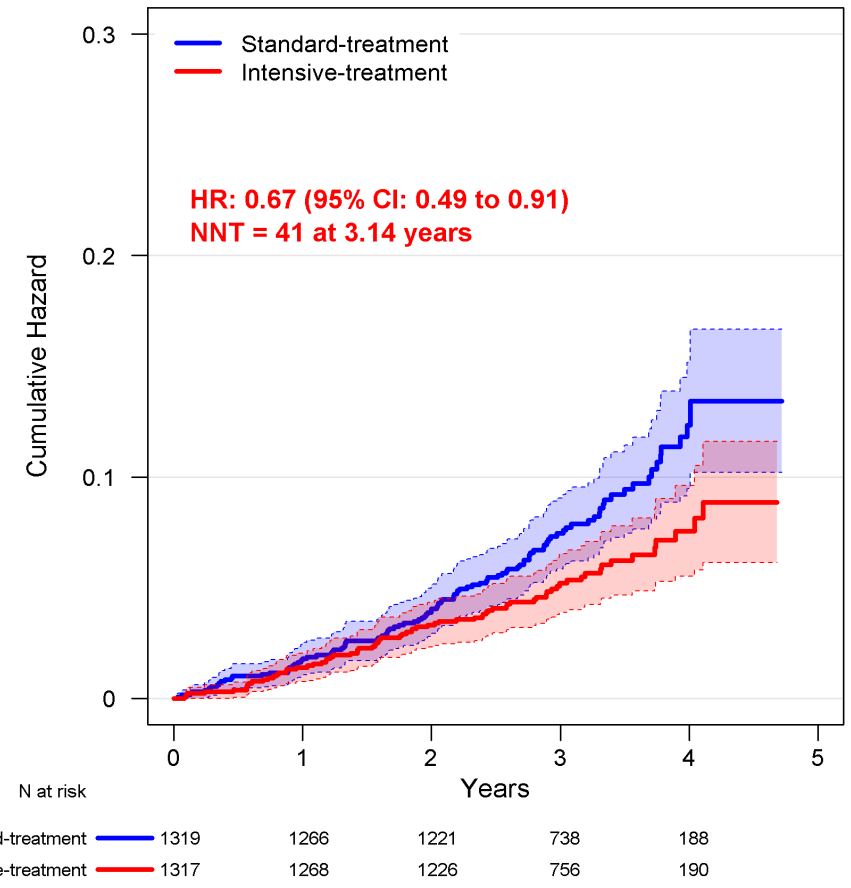
# of Participants

Cumulative Hazards for SPRINT Outcomes in Participants 75 and older

Primary Outcome

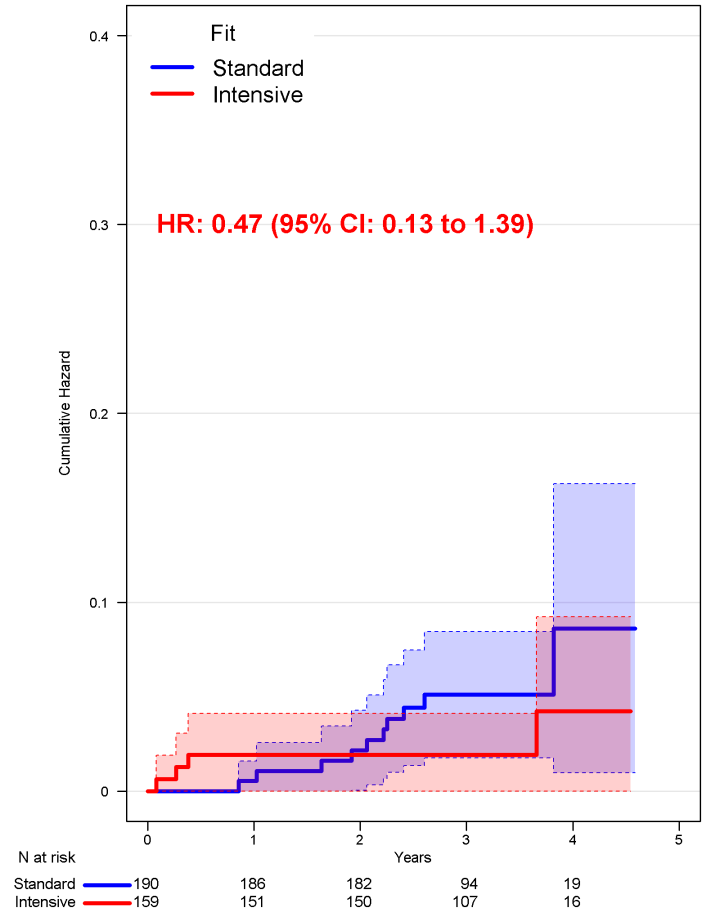


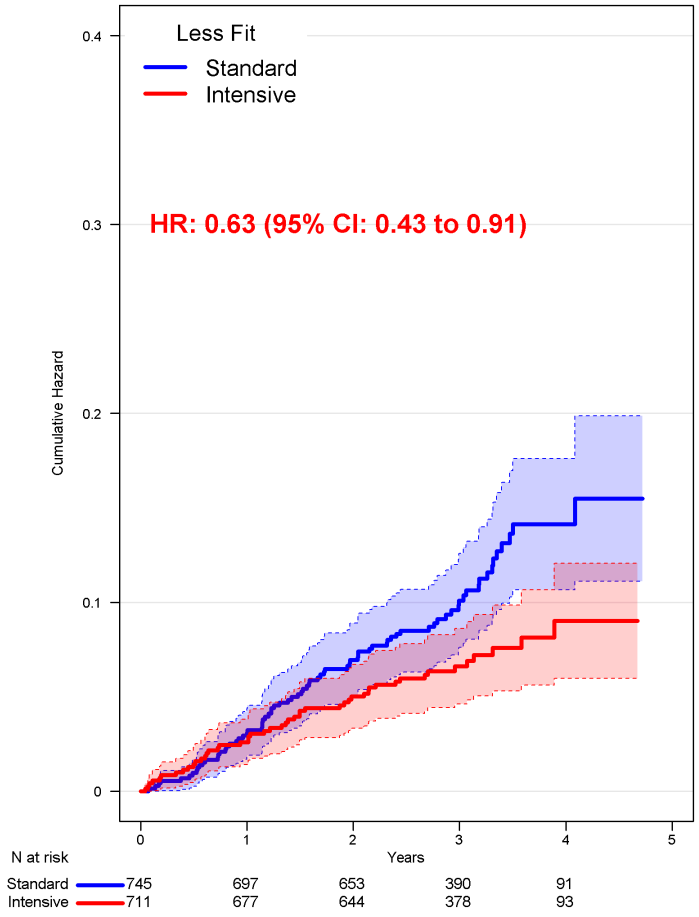
All-Cause Mortality

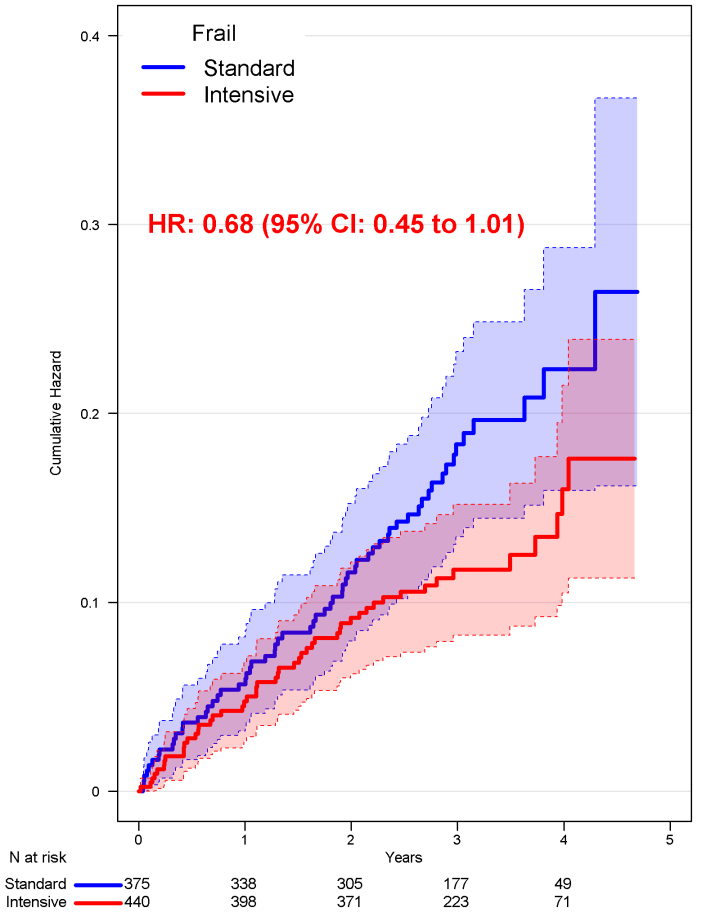


Primary outcome includes non-fatal myocardial infarction (MI), acute coronary syndrome not resulting in MI, non-fatal stroke, non-fatal acute decompensated heart failure, and CVD death.

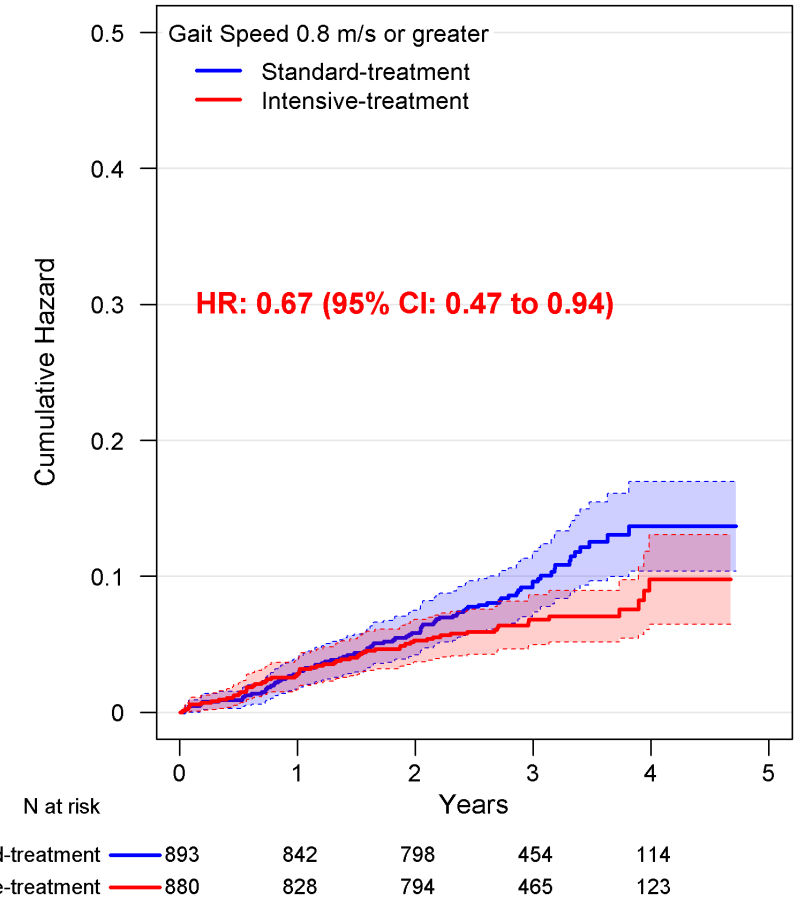
Cumulative Hazards for SPRINT Primary Outcome by Frailty Status

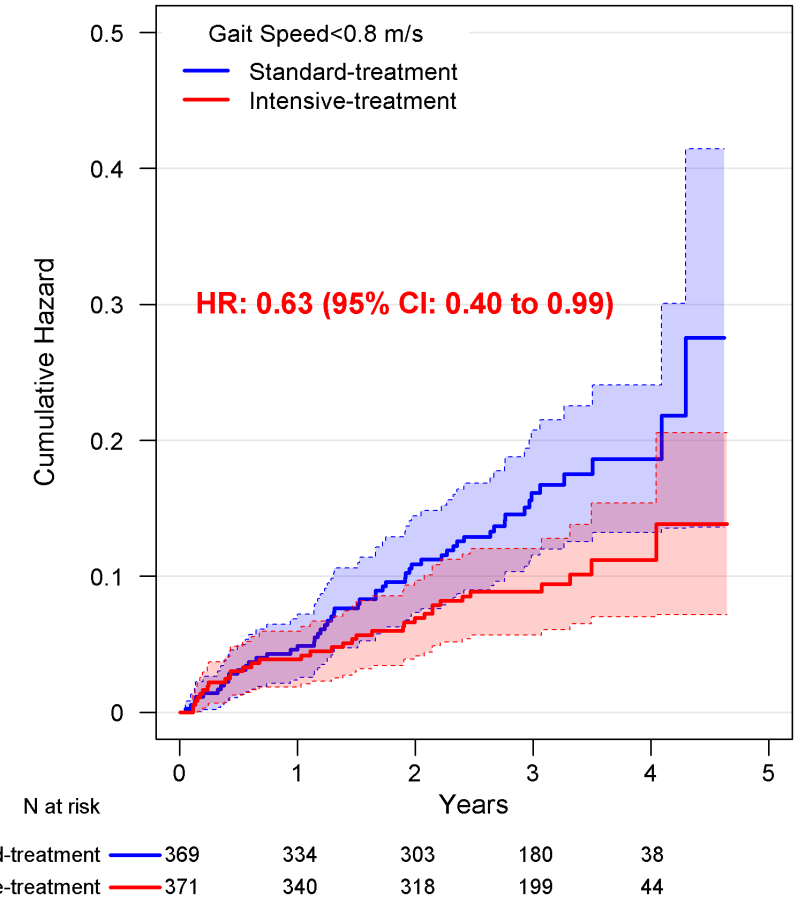






Cumulative Hazards for SPRINT Primary Outcome by Gait Speed



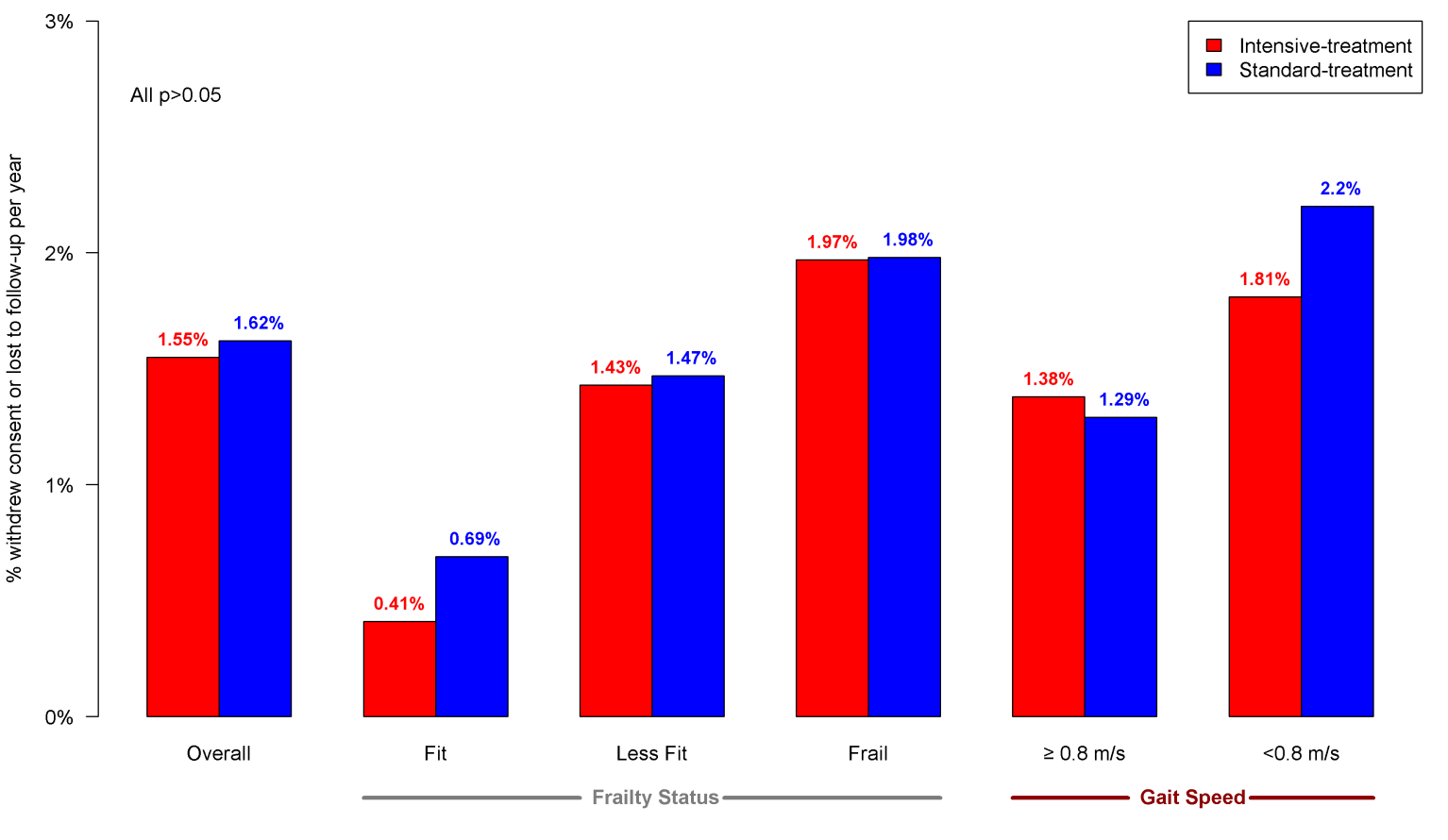


SPRINT Follow-up Experience: Withdrawn Consent & Loss to Follow-up

	Intensive-treatment		Standard-treatment			
	N	%/year	N	%/year	HR (95% CI)	p-value
Overall	62	1.55 (1.21, 1.99)	64	1.62 (1.27, 2.07)	1.04 (0.73, 1.47)	0.846
Frailty Status						
Fit	2	0.41 (0.10, 1.62)	4	0.69 (0.26, 1.85)	0.76 (0.13, 4.37)	0.756
Less fit	31	1.43 (1.01, 2.03)	33	1.47 (1.04, 2.06)	1.02 (0.63, 1.66)	0.933
Frail	26	1.97 (1.34, 2.89)	22	1.98 (1.30, 3.00)	1.11 (0.64, 1.92)	0.717
Gait Speed						
≥0.8 m/s	37	1.38 (1.00, 1.91)	35	1.29 (0.93, 1.80)	1.12 (0.70, 1.78)	0.637
<0.8 m/s	20	1.81 (1.17, 2.81)	24	2.20 (1.47, 3.28)	0.87 (0.48, 1.57)	0.645
Missing	5	2.38 (0.99, 5.71)	5	3.08 (1.28, 7.41)	1.30 (0.33, 5.23)	0.708

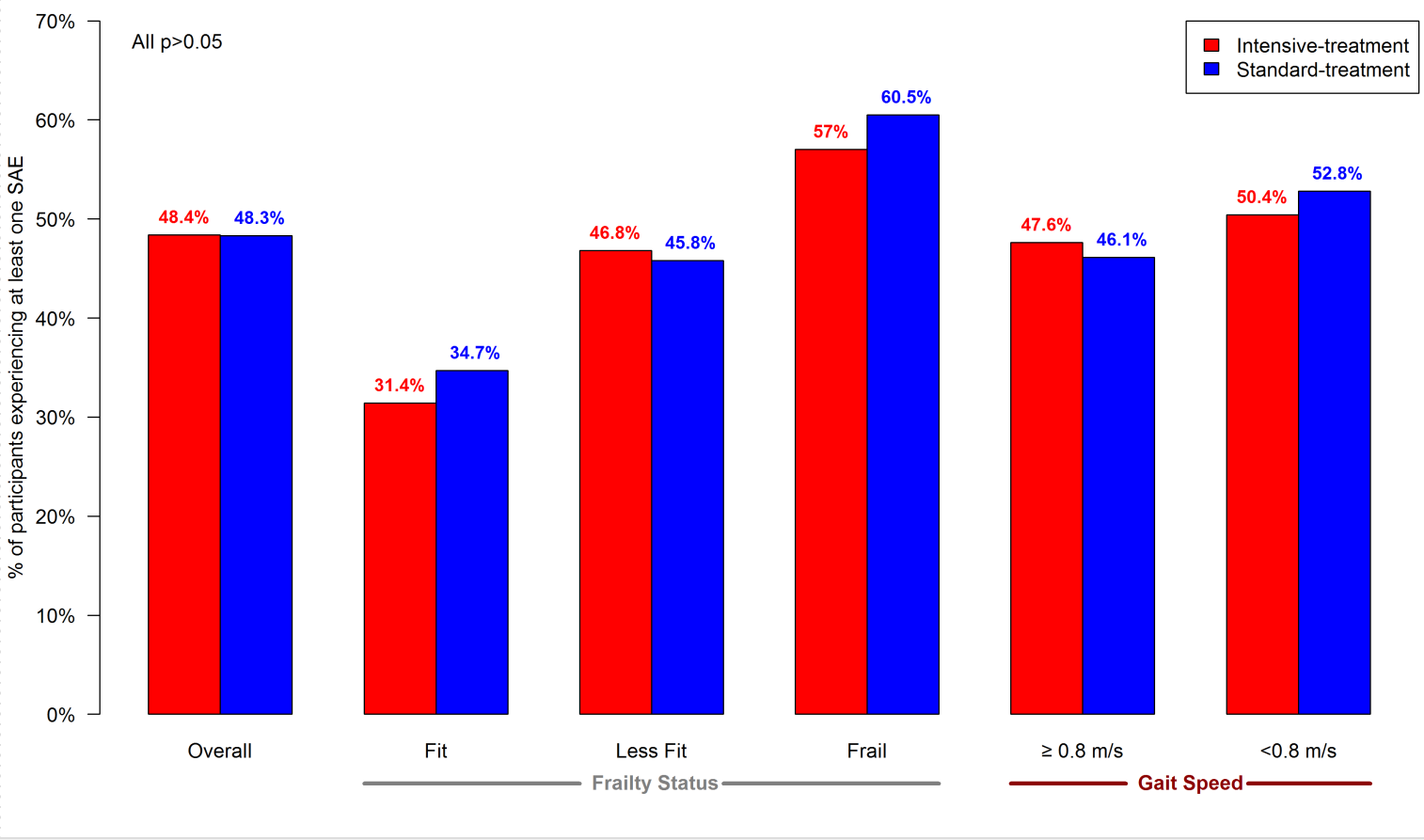
(%/year) Percentage of participants withdrawing consent or lost to follow-up per year. (HR) Hazard Ratio based on competing risks model accounting for death.

SPRINT Follow-up Experience: Withdrawn Consent & Loss to Follow-up



(%/year) Percentage of participants withdrawing consent or lost to follow-up per year. (HR) Hazard Ratio based on competing risks model accounting for death.

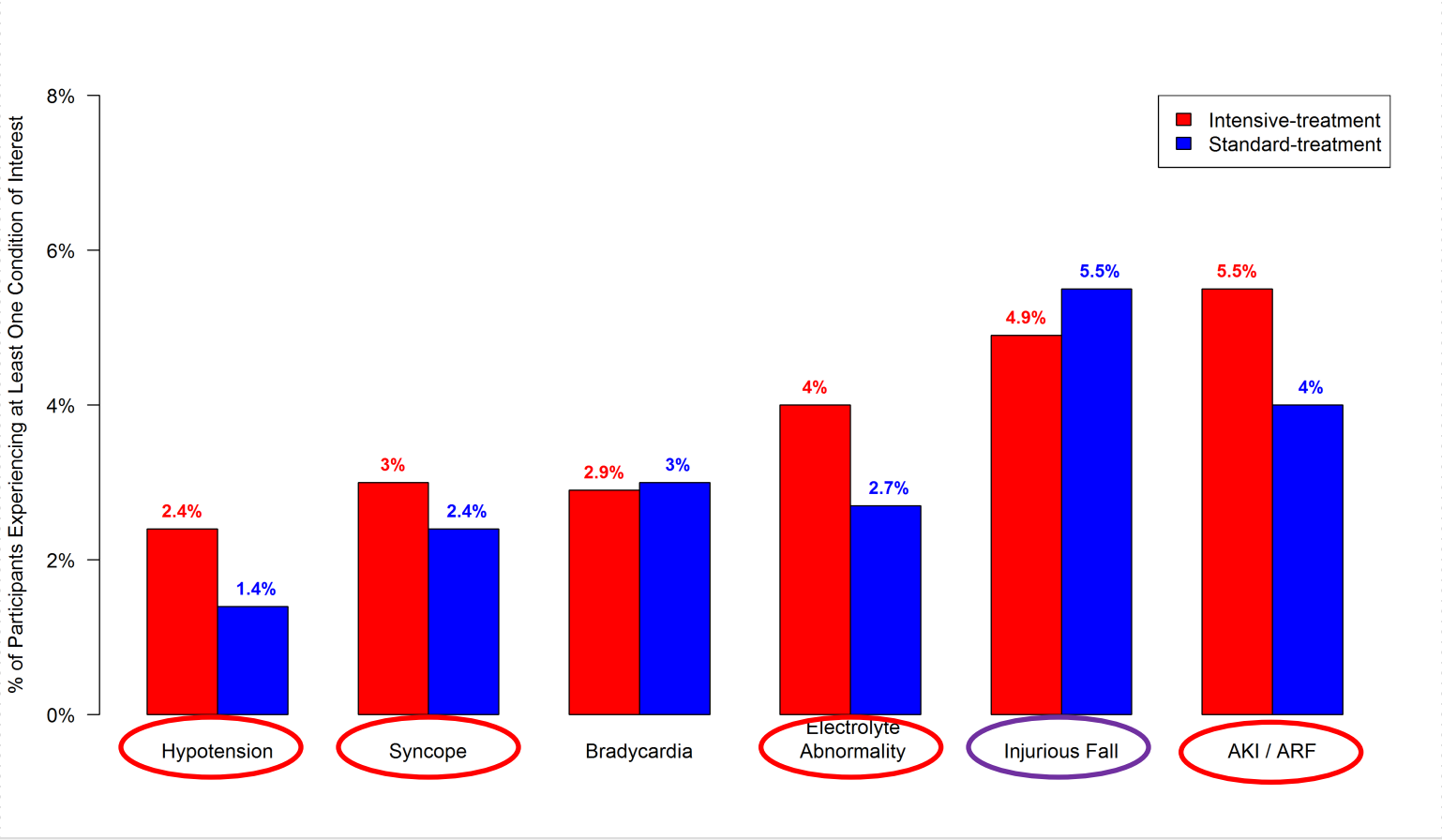
Serious Adverse Events, by treatment group in SPRINT participants > 75 years



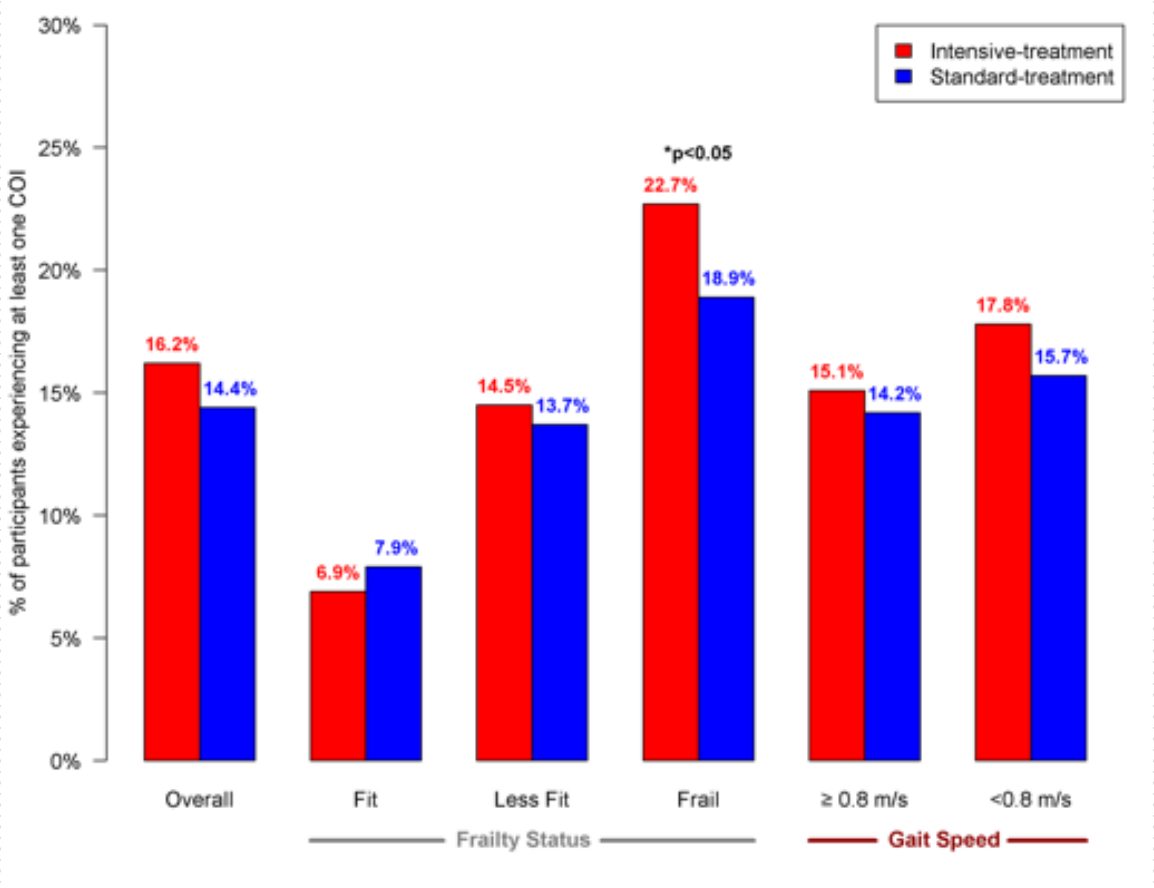
Conditions of Interest for Participants > 75 Years

	Intensive-treatment N with event (%)	Standard-treatment N with event (%)	HR (95% CI)	p-value
Conditions of Interest	214 (16.2)	190 (14.4)	1.18 (0.97, 1.44)	0.106
Hypotension	32 (2.4)	19 (1.4)	1.71 (0.97, 3.09)	0.066
Syncope	39 (3.0)	32 (2.4)	1.23 (0.76, 2.00)	0.401
Bradycardia	38 (2.9)	40 (3.0)	0.89 (0.57, 1.40)	0.610
Electrolyte Abnormality	53 (4.0)	36 (2.7)	1.51 (0.99, 2.33)	0.058
Injurious Fall	65 (4.9)	73 (5.5)	0.91 (0.65, 1.29)	0.605
Acute Kidney Injury or Acute Renal Failure	72 (5.5)	53 (4.0)	1.41 (0.98, 2.04)	0.061

Conditions of Interest for Participants > 75 Years



Conditions of Interest for Participants > 75 Years By Frailty Status and Gait Speed

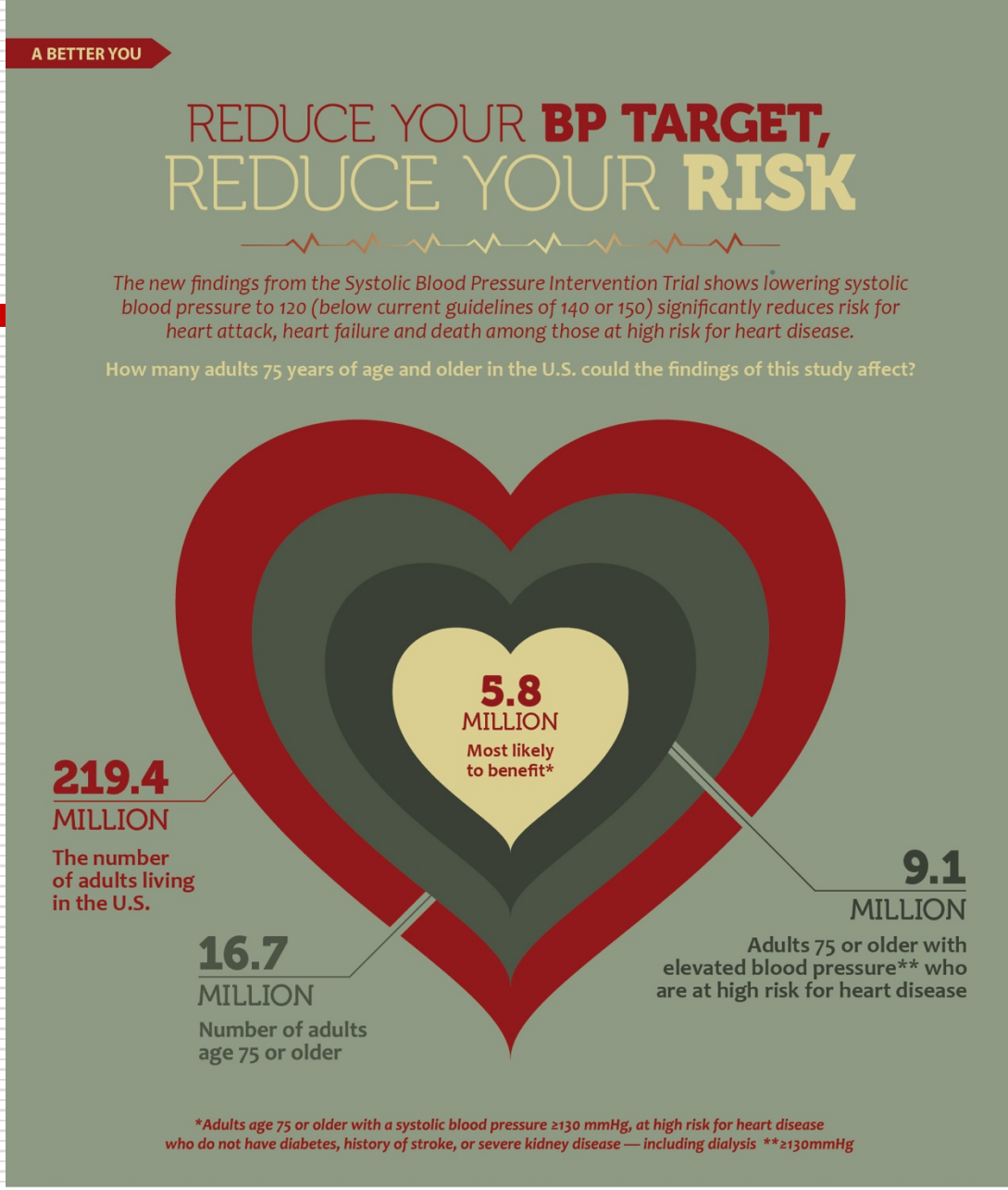


Number of Participants with a Monitored Clinical Measure During Follow-up

	Intensive-treatment N with event (%)	Standard-treatment N with event (%)	HR (95% CI)	p-value
Monitored Clinical Events				
Laboratory Measures				
Sodium<130 mmol/L	69 (5.2)	45 (3.4)	1.56 (1.07, 2.30)	0.02
Sodium>150 mmol/L	1 (0.1)	0 (0.0)	-	-
Potassium<3 mmol/L	17 (1.3)	11 (0.8)	1.50 (0.69, 3.37)	0.303
Potassium>5.5 mmol/L	69 (5.2)	65 (4.9)	1.01 (0.71, 1.42)	0.972
Signs and Symptoms				
Orthostatic hypotension	277 (21.0)	288 (21.8)	0.90 (0.76, 1.07)	0.241
Orthostatic hypotension with dizziness	25 (1.9)	17 (1.3)	1.44 (0.77, 2.73)	0.252

Generalizability

Who may benefit?



Generalizability of results from the Systolic Blood Pressure Intervention Trial (SPRINT) to the US adult population

Journal of the American College of Cardiology online, No. 9, 2015

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Conclusions

- The SPRINT-Senior cohort is representative of community dwelling older adults
- Rates of hypotension, syncope, electrolyte abnormalities, kidney injury were higher in the intensive arm, but not rates of injurious falls or orthostatic hypotension
- Overall, benefits of more intensive BP lowering – 33% reduction in primary CV outcome and 32% reduction in total mortality – exceeded the potential for harm, even among the most frail older patients

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)

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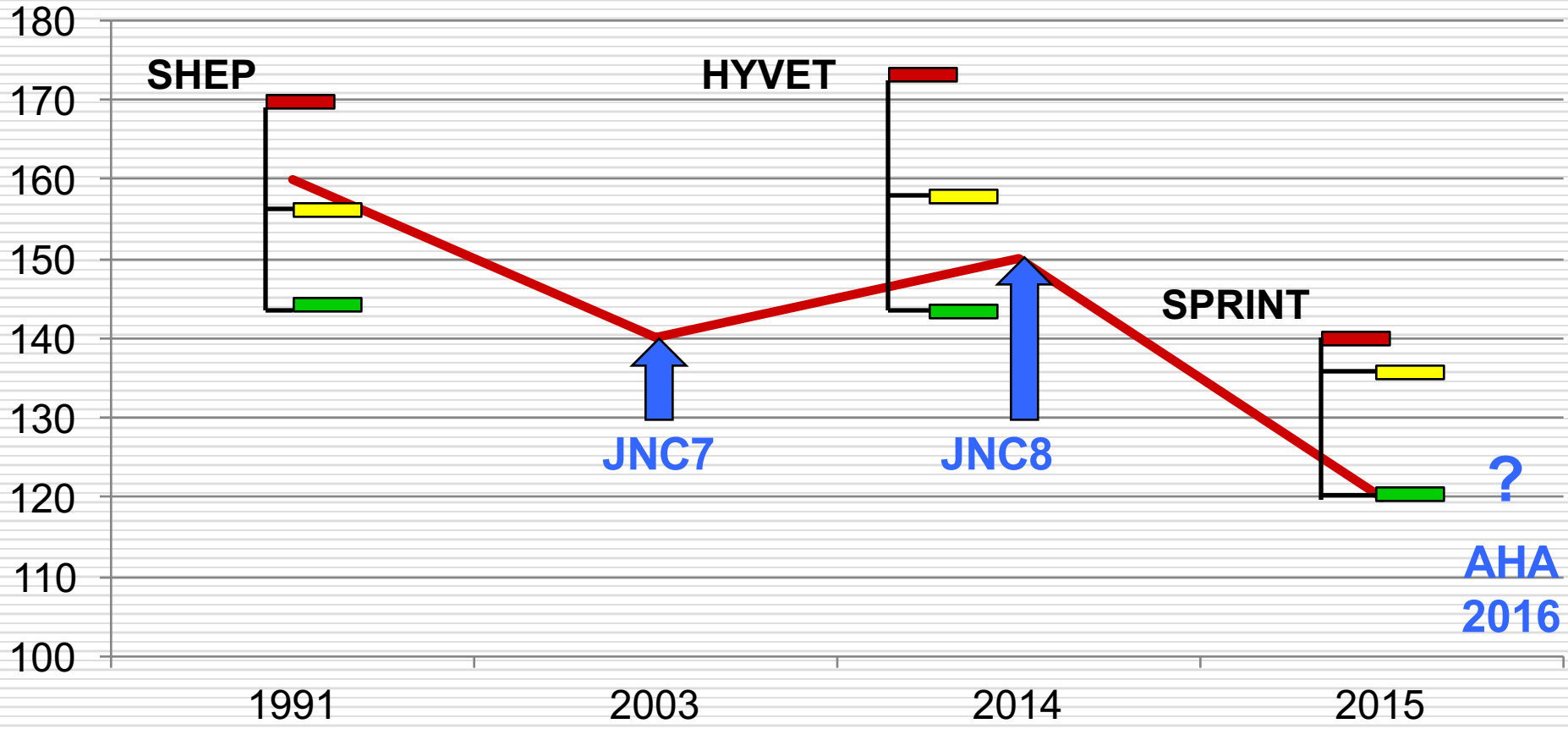
Questions...

Forthcoming SPRINT Results

- SPRINT-MIND Cognitive and brain MRI outcomes
- Renal
- Health related quality of life
- Adverse events (nursing home placement), safety (falls, orthostasis), cost analysis

Healthy age 60 to 80+: What SBP Target?



Caveats

- Exclusions:
  - Diabetes, stroke, heart failure
  - Standing BP < 110 mm Hg
  - Community living, ambulatory
- BP measurement protocol

Frailty Status in HYVET

- Frailty index distribution in HYVET matches general population > 80 years
- No evidence interaction between effect of treatment and frailty
- "Both the frailer and the fitter older adults with hypertension appeared to gain from treatment."

Frailty index adjusted treatment effects (n=2,656)

Stroke	CV Events	Total Mortality
0.64 (0.42–0.96)	0.59 (0.45–0.77)	0.83 (0.66–1.04)

Hazard ratios (95% CI)

Warwick et al. BMC Medicine (2015) 13:78