

A Function-Based Approach to Treating Elevated Blood Pressure in Older Adults

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A Treatment Conundrum

December 2014

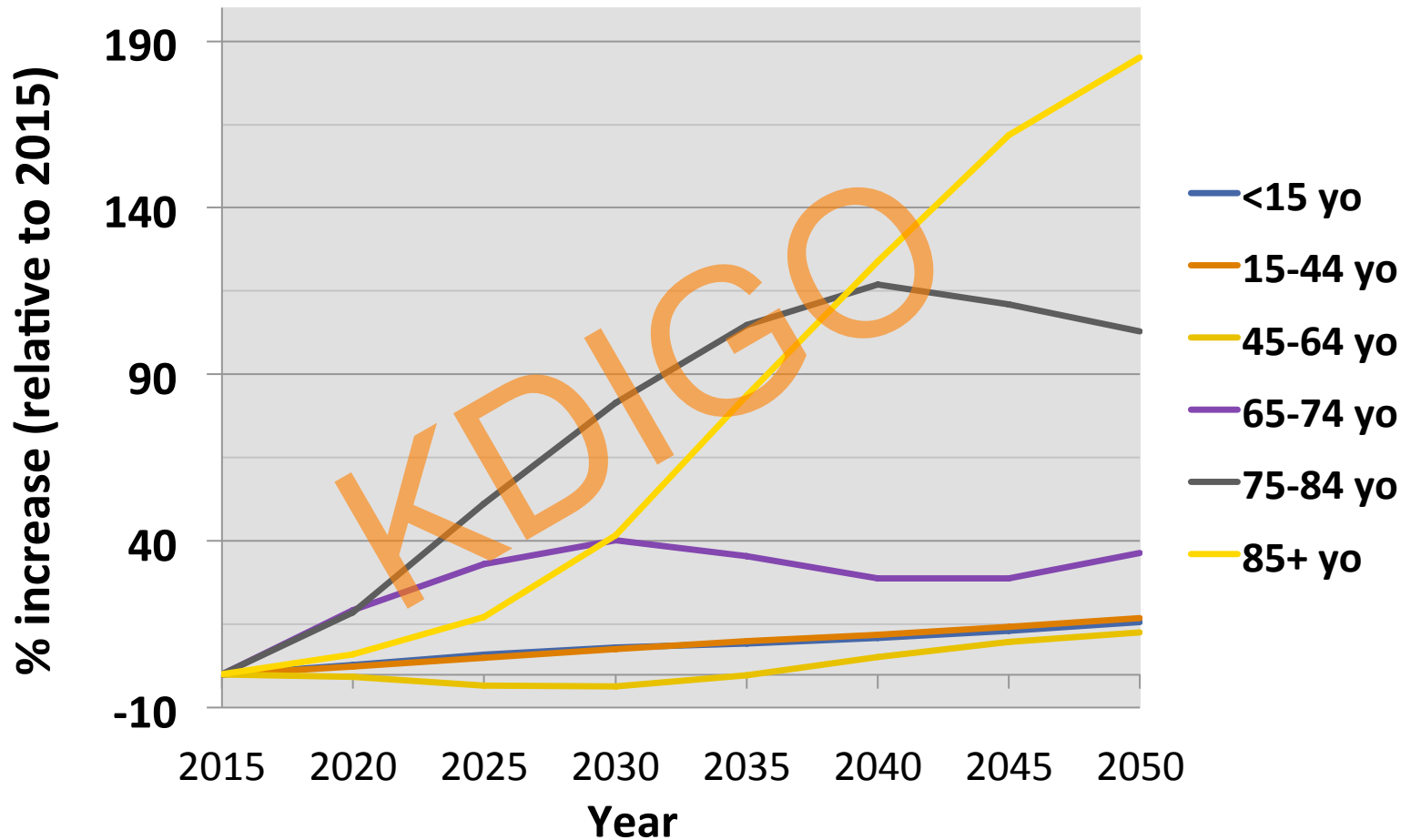
- Mrs. M.S., an 84 year old grandmother
- Hypertension, prior MI, OA, mild incontinence, GERD
- Uses cane to walk in grocery store with daughter; fell once 2 months ago, Serum creatinine = 1.7, Hgb A1C=6.1
- Main goal: attend granddaughter's wedding (ring expected at Valentine's day 2015)
- On 1 med for elevated SPB
- BP in office = 144 mm Hg & 5 mm Hg drop on standing no symptoms.
- What to do?



Age 60 to 100: What Should be the Systolic Blood Pressure Target?

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

Projected Percent Growth in US Population by Age, 2015 to 2050



Williamson's Key Goals of Aging-related Research and Clinical Care

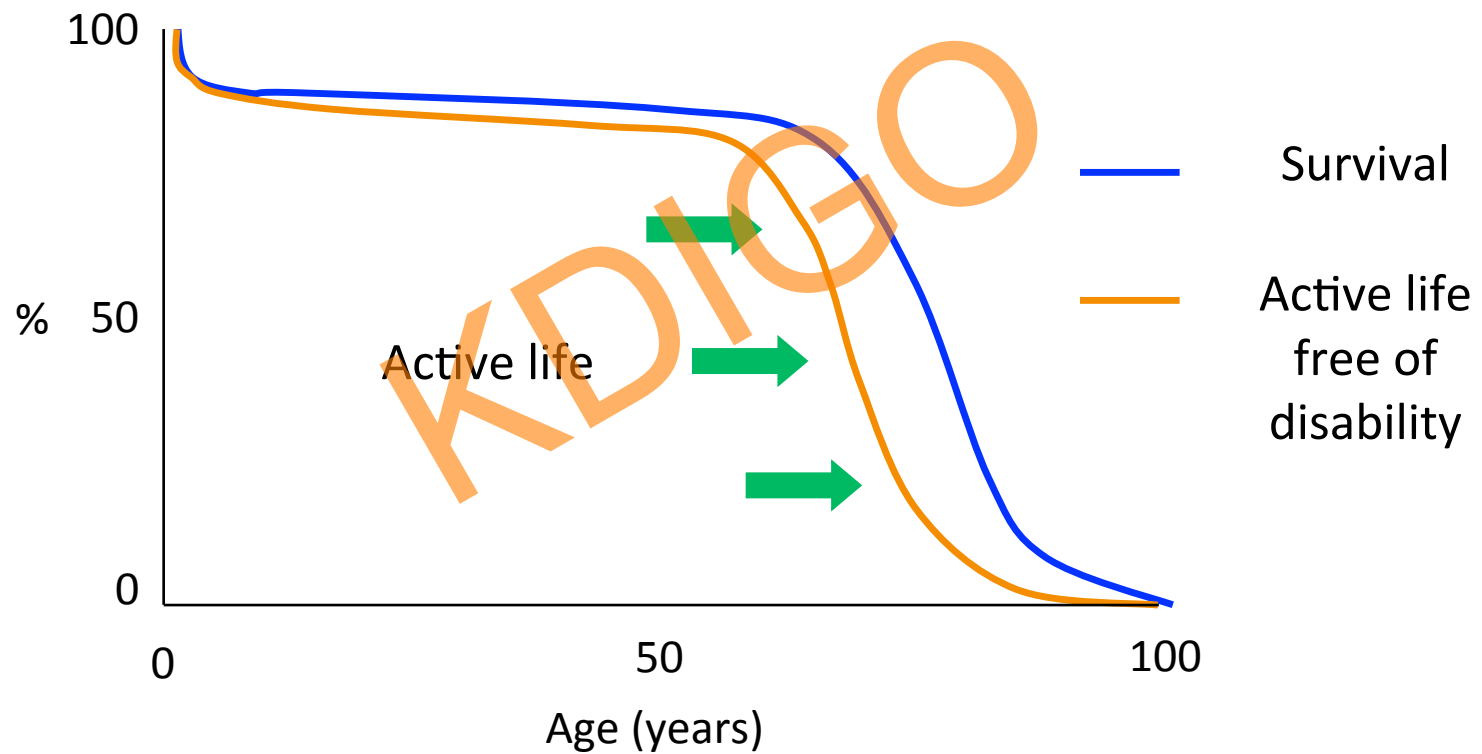
Preventing 2 of the primary reasons why older adults move to a nursing home:

1. Brain failure: cognitive function
2. Leg Failure: physical Function

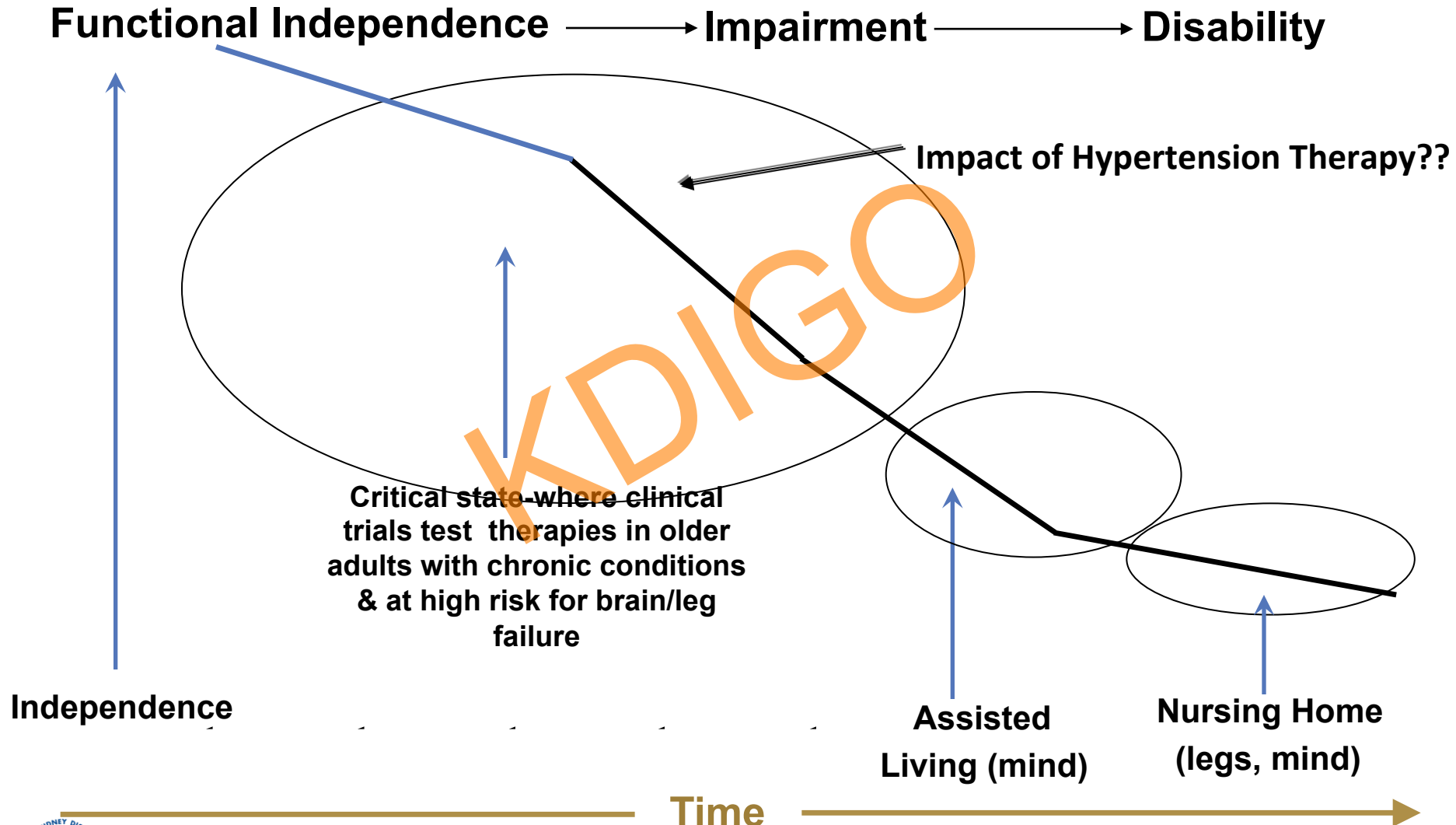
Function-based and multifactorial



Primary Focus of Aging Research and Clinical Care : To Expand Active Life Expectancy



Trajectory of Functional Disability



Premise (Prejudice)

- There is an aspect of health which is more than the lack (or presence) of pathology in individual organs.
- Functional measures are more valuable than age specifically because they tap how a patient is doing as an “integrated system.”

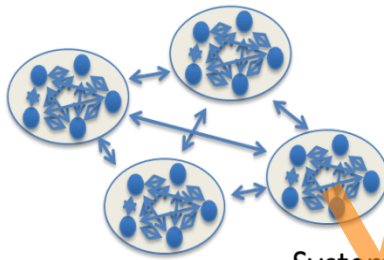
Steve Krichevsky, PhD

What is slow gait or poor cognition a sign of?

The Patient's Lived Experience



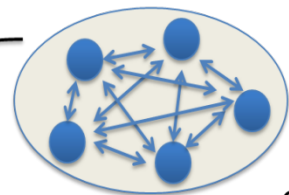
Focus of Geriatrics



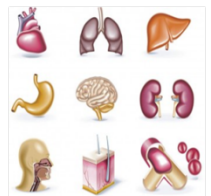
Systems of Organs



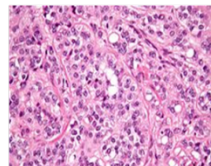
Focus of Subspecialty Medicine



Organ



Cells



Restricted Life Space

Fatiguability

Depression

Self-Rated Health

Pain

IL-6

Circulating Mito Resp. Capacity

Cognitive Speed / Function

VO2 Max

White Matter Burden

Low EGFR / High Cystatin C

FEV1

Anemia

Cardiac Output

Muscle perfusion

Muscle strength

Motor Units

Capillary Density

Type I : Type II Fiber Ratio

Neuromuscular Junction

Troponin Splice Variants

Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia

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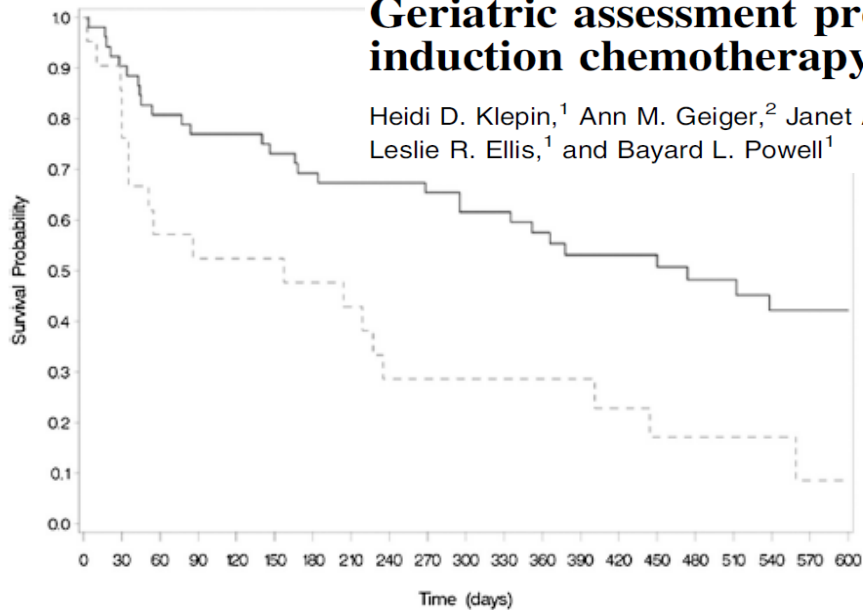


Figure 2. Baseline cognitive function is associated with worse OS among older adults treated for AML (N = 73). Median survival differed using log-rank testing.

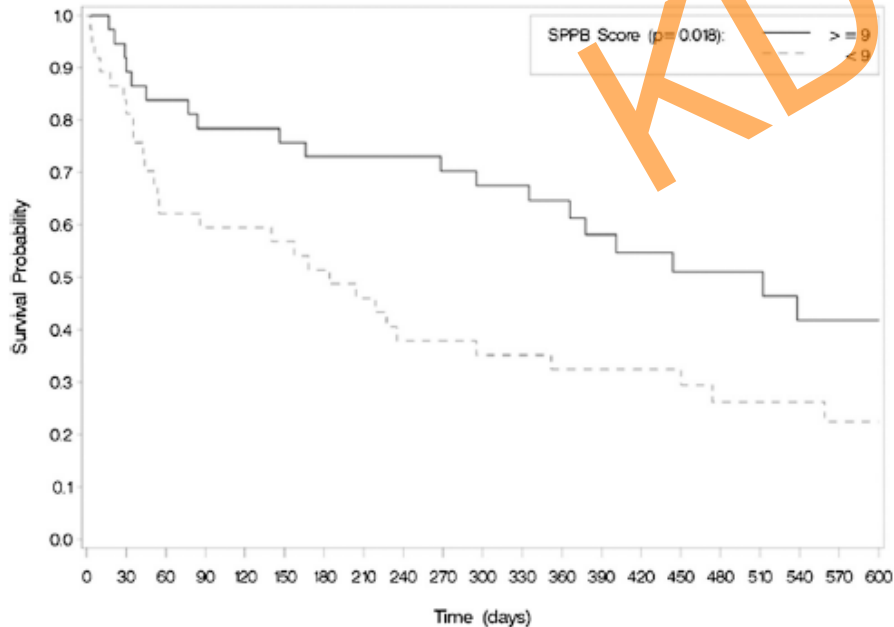


Figure 3. Impaired physical performance is associated with worse OS among older adults treated for AML (N = 74). Median survival differed using log-rank testing.

Table 3. Association between clinical characteristics, baseline GA measures, and OS among older adults with AML (N = 73)

Baseline characteristics	Hazard ratio for mortality (95% CI)	
	Unadjusted	Adjusted*
Clinical and demographic characteristics		
Age (per 10-y change)	1.1 (0.7-1.7)	1.3 (0.8-2.0)
Education (reference < high school)		
High school	0.9 (0.4-2.0)	0.9 (0.3-2.6)
College	0.8 (0.4-1.5)	0.8 (0.3-1.8)
ECOG score (continuous)	1.5 (0.9-2.4)	1.2 (0.7-1.9)
Hemoglobin (continuous)	0.8 (0.7-1.0)	0.7 (0.6-0.9)
LDH (≥600)	0.5 (0.2-1.4)	0.6 (0.2-1.5)
White blood cell count (≥25 000)	0.8 (0.4-1.6)	1.3 (0.6-3.0)
Cytogenetic risk group (favorable/intermediate)	0.5 (0.3-0.8)	0.3 (0.2-0.7)
Prior MDS (not present)	0.5 (0.3-0.8)	0.4 (0.2-0.7)
GA measures		
Cognitive impairment (3MS < 77)	2.4 (1.3-4.4)	2.5 (1.2-5.5)
Depressive symptoms (CES-D score ≥16)	1.4 (0.8-2.5)	1.0 (0.5-2.0)
Distress (score < 4)	1.2 (0.6-2.1)	1.0 (0.5-1.8)
IADL impairment (any at the time of treatment)	1.3 (0.7-2.2)	0.8 (0.4-1.6)
ADL impairment (any at the time of treatment)	1.3 (0.7-2.1)	1.1 (0.5-2.1)
Mobility impairment (any at the time of treatment)	1.4 (0.7-2.6)	1.0 (0.5-2.1)
Impaired physical performance (SPPB < 9)	1.9 (1.1-3.4)	2.2 (1.1-4.6)
Comorbidity burden (HCT-CI > 1)	1.5 (0.9-2.7)	1.2 (0.7-2.2)

One subject with missing cytogenetic risk group data was excluded.

ADL, activities of daily living; IADL, instrumental activities of daily living; LDH, lactate dehydrogenase.

*Adjusted model includes age, gender, ECOG performance status, cytogenetic risk group, prior MDS, and hemoglobin.

BLOOD, 23 MAY 2013 • VOLUME 121, NUMBER 21

Gait Speed as a Stress Resistance Indicator

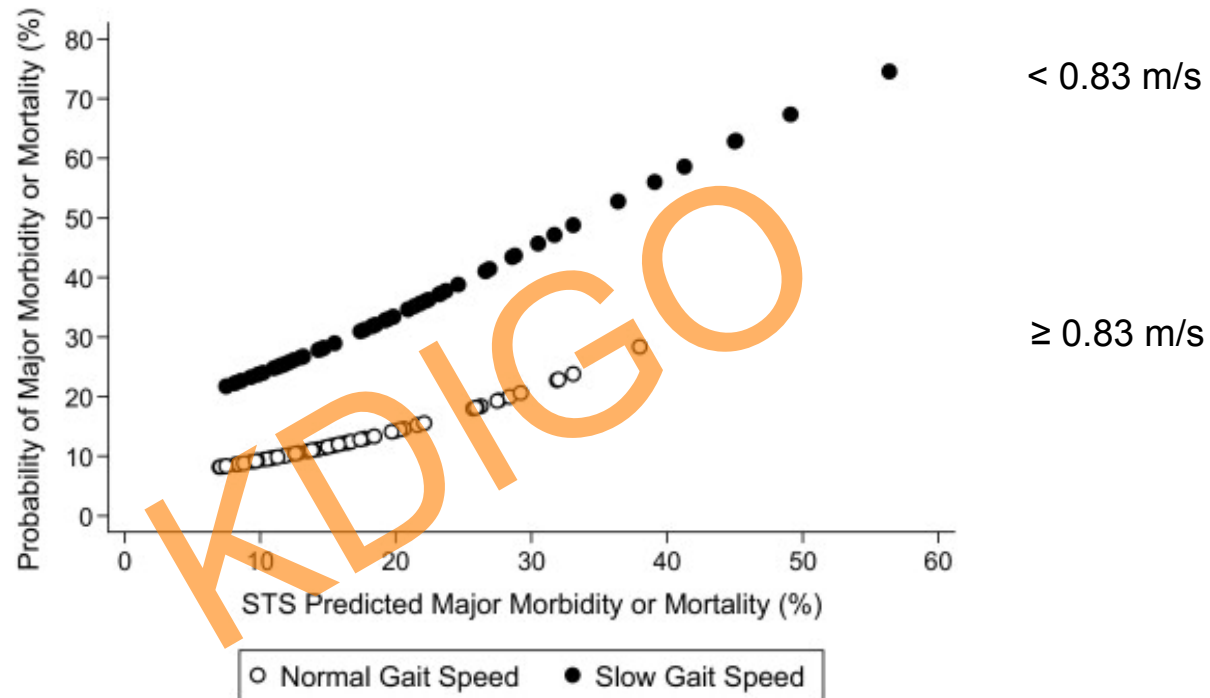


Figure 3 Predicted Probability of Mortality or Major Morbidity According to Gait Speed and the STS Risk Score Slow gait speed (solid circles) conferred a 2- to 3-fold increase in risk for any given level of Society of Thoracic Surgeons (STS) predicted m...

Outcome: post-op death, stroke, renal failure, prolonged ventilation, sternal wound infection, need for reoperation.

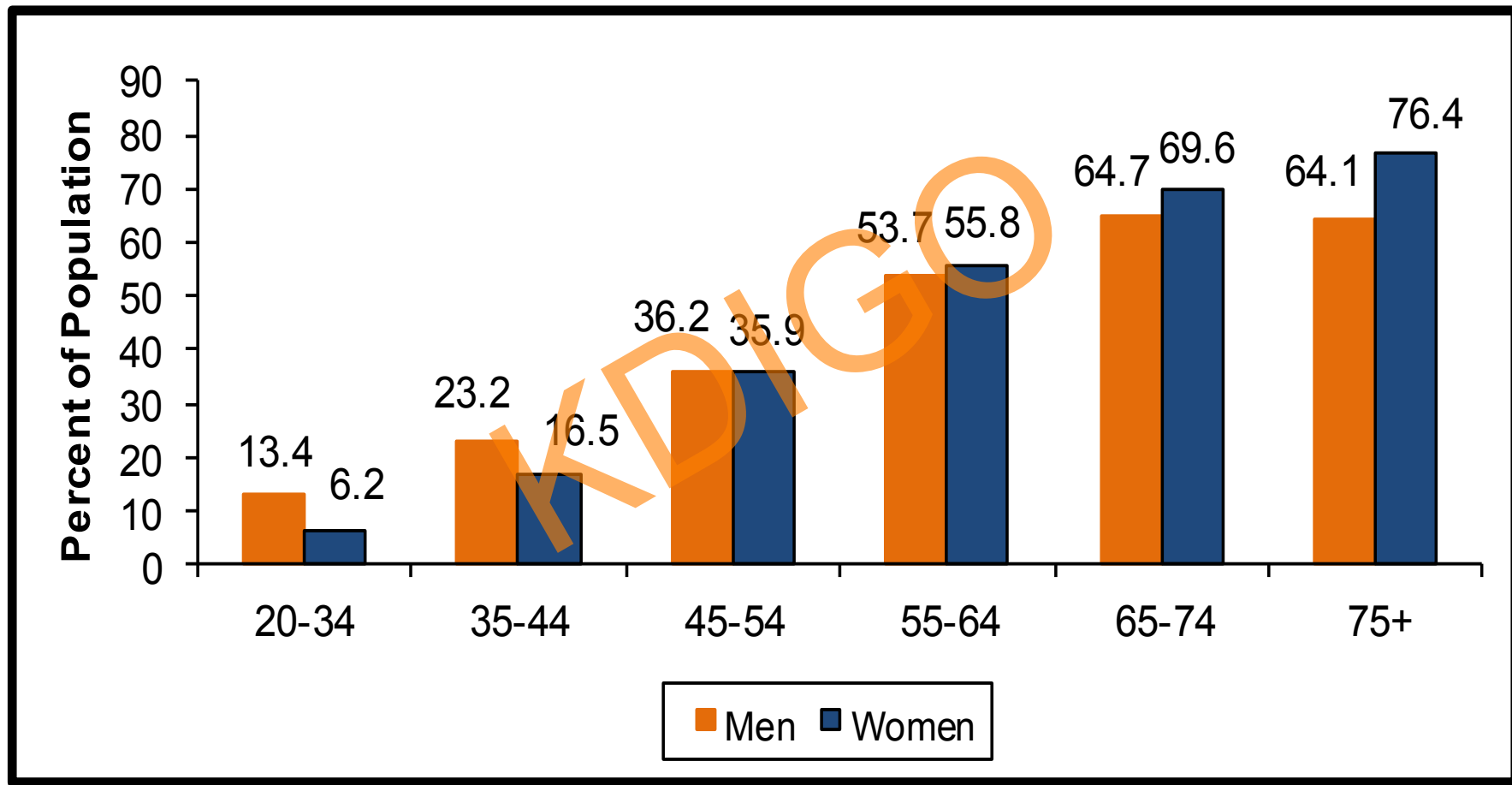
Jonathan Afilalo , Mark J. Eisenberg , Jean-François Morin , Howard Bergman , Johanne Monette , Nicolas Noiseux , ...

Gait Speed as an Incremental Predictor of Mortality and Major Morbidity in Elderly Patients Undergoing Cardiac Surgery

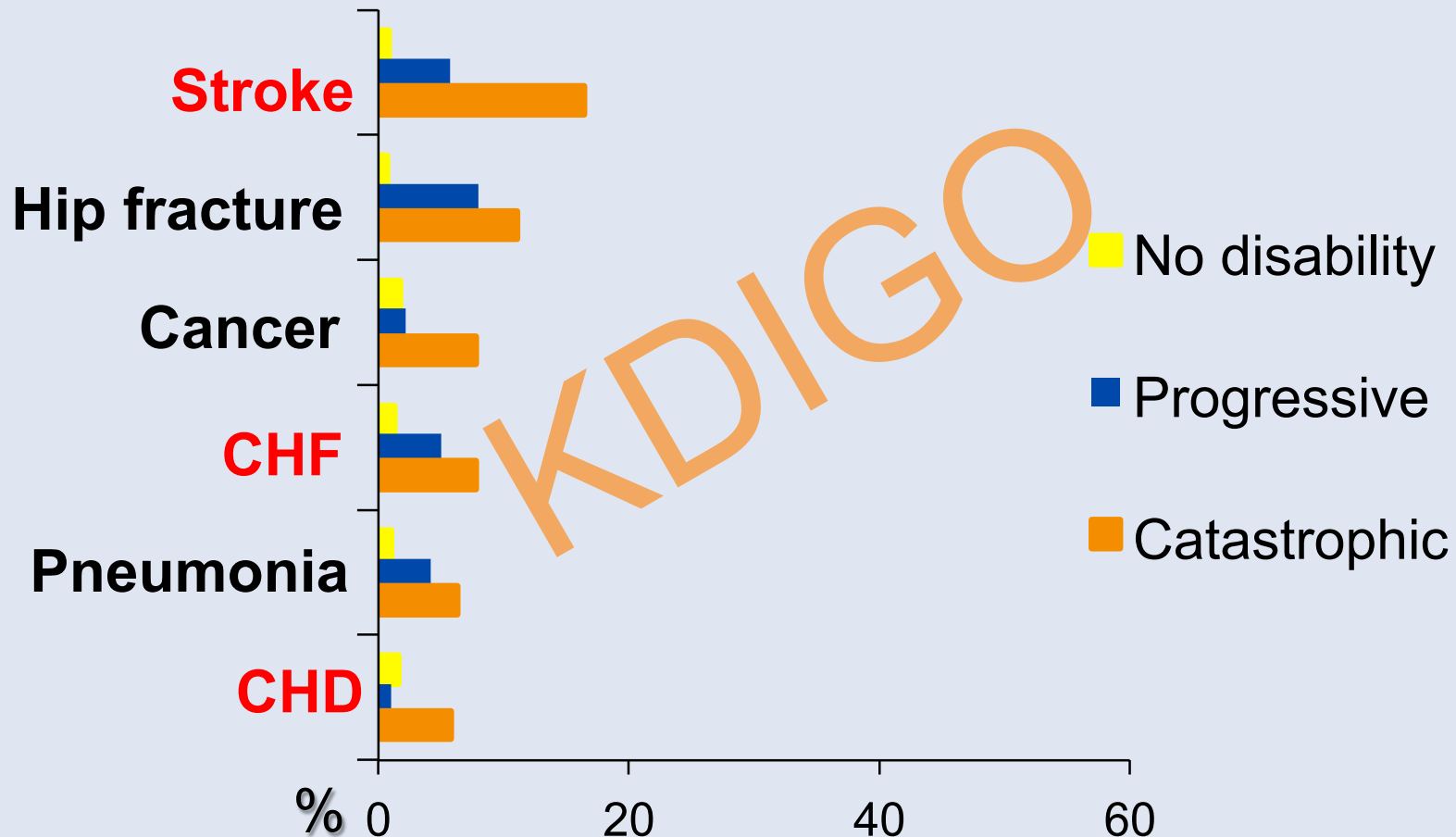
Journal of the American College of Cardiology, Volume 56, Issue 20, 2010, 1668 - 1676

Wake Forest Baptist Medical Center
<http://dx.doi.org/10.1016/j.jacc.2010.06.039>

Prevalence of High Blood Pressure in Adults by Age and Sex



EPESE: Hospital Diagnoses in the Year When Older Persons become Disabled



Ferrucci, et al. *JAMA* 1997;277:728

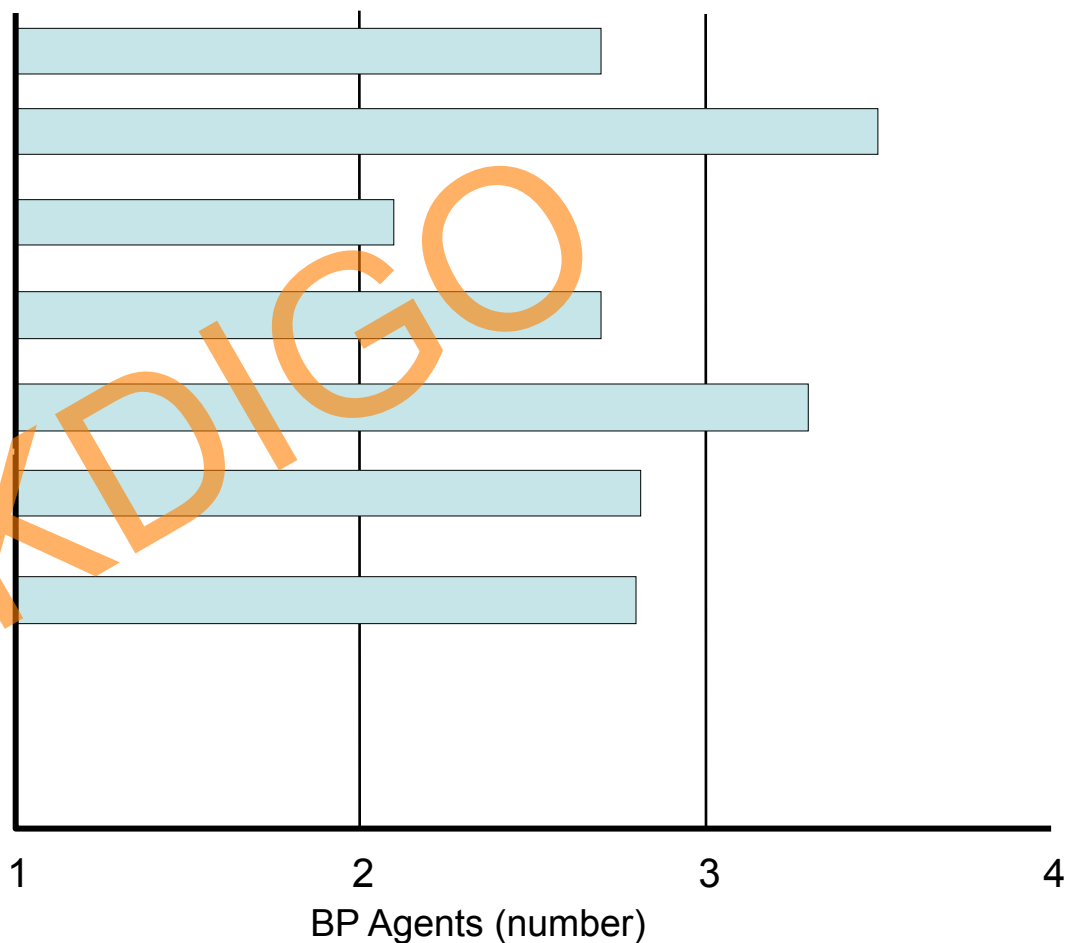
KDIGO Controversies Conference on Blood Pressure in CKD
September 7-10, 2017 | Edinburgh, Scotland



Combination Therapy Is Needed to Achieve Target SBP Goals

Trial (SBP Achieved)

UKPDS	(144 mm Hg)
RENAAL	(141 mm Hg)
ALLHAT	(138 mm Hg)
IDNT	(138 mm Hg)
HOT	(138 mm Hg)
INVEST	(133 mm Hg)
ABCD	(132 mm Hg)
MDRD	(132 mm Hg)
AASK	(128 mm Hg)



SBP = systolic blood pressure.

Conflicting Data about Anti-HTN Treatment and Falls

Study	Population	Falls Type	Drugs	Dose	Falls Rate
Tinetti, 2014	Medicare Beneficiaries	1. Injurious 2. Inj, fallers	All	1. Mod intense 2. Hi Intensity	1. Increased 2. Increased
Wong, 2013	Community-dwelling	All	1. Renin-Angio 2. Other CV Rx	Not reported	1. Decreased 2. No effect
Callisaya, 2014	Community-dwelling	All	All	1. Therapeutic 2. 3X DDD	1. No effect 2. Increased
Lipsitz, 2015	Community-dwelling	Inj, Outdoor All, Indoor	1. ACE 2. CCB 3. All others	High doses High Doses Any dose	1. Decreased 2. Decreased 3. No effect
Margolis, 2014	T2 Diabetes, ACCORD	1. All 2. Fx: Non-spine	All	SBP < 120 vs SBP < 140	1. No effect 2. Decreased

SPRINT Research Question

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

Target Systolic BP

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graph TD; A[Target Systolic BP] --> B[Intensive Treatment Goal SBP < 120 mm Hg]; A --> C[Standard Treatment Goal SBP < 140 mm Hg];
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Intensive Treatment
Goal SBP < 120 mm Hg

Standard Treatment
Goal SBP < 140 mm Hg

SPRINT design details available at:

- [ClinicalTrials.gov \(NCT01206062\)](https://clinicaltrials.gov/ct2/show/study/NCT01206062)
- Ambrosius WT et al. *Clin Trials* 2014;11:532-546.

Pre-specified Subgroups of Special Interest

- Age (<75 vs. ≥ 75 years)
- Gender (Men vs. Women)
- Race/ethnicity (Black vs. non-Black)
- Chronic Kidney Disease (eGFR <60 vs. ≥ 60 mL/min/1.73m²)
- CVD (Prior CVD vs. no prior CVD)
- Level of BP (Baseline SBP tertiles: ≤ 132 , 133 to 144, ≥ 145 mm Hg)

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-yr Framingham CVD risk, %	20.1%	20.1%	20.1%
Not taking antihypertensive meds, %	9.4%	9.2%	9.6%
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)

Baseline Characteristics: Participants 75 years or older (n=2,636)

	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 (mm Hg)			
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)

Additional Outcomes

- All-cause mortality
- Primary outcome + all-cause mortality
- Dementia /Mild Cognitive Impairment
- Brain MRI for small vessel ischemic disease
- Renal Outcome
 - Participants with CKD at baseline: $\geq 50\%$ decline in eGFR or ESRD (primary renal outcome)
- Health-related quality of life assessments
- Ancillary studies
 - Arterial stiffness and central blood pressure
 - Ambulatory blood pressure

Additional Geriatrics-Focused Measures

- Assessments
 - Gait speed – 4 m walk
 - Only collected in those 75+ years at baseline
- Frailty status (Rockwood)
- Adverse Events
 - PHQ-9
 - Falls and injurious falls
 - Orthostatic hypotension +/- dizziness
 - Hospitalizations
 - Nursing home placement

Importance of Assessing Frailty

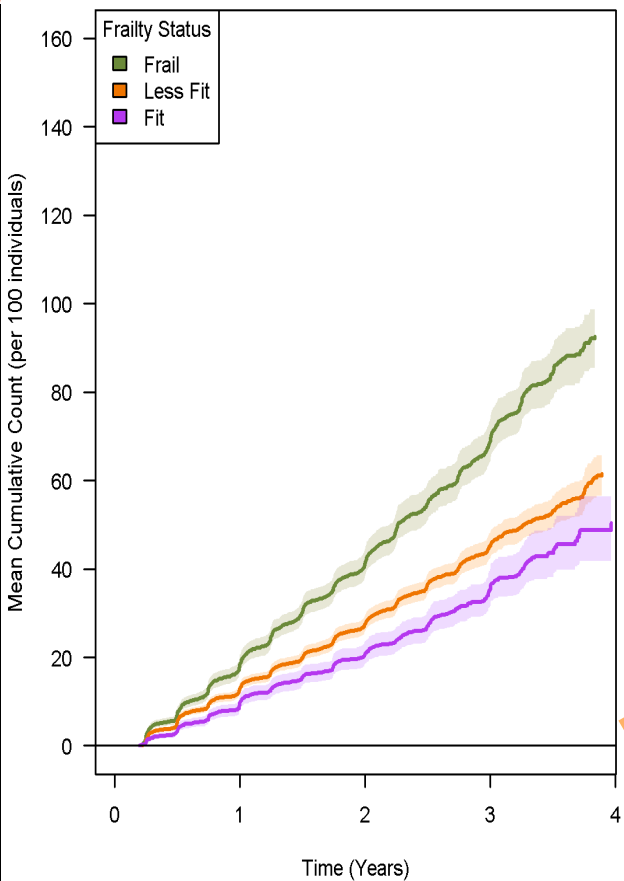
- Translation of clinical trial results into clinical practice
- Concerns about selection biases and generalizability of trial cohorts, especially for geriatric populations¹
- Concerns about falls and potential impact on cognition
- Concerns that trial cohorts are healthier, have less co-morbidity, are less frail, which perhaps limits external validity to clinical practice

Baseline Characteristics: Participants 75 years or older

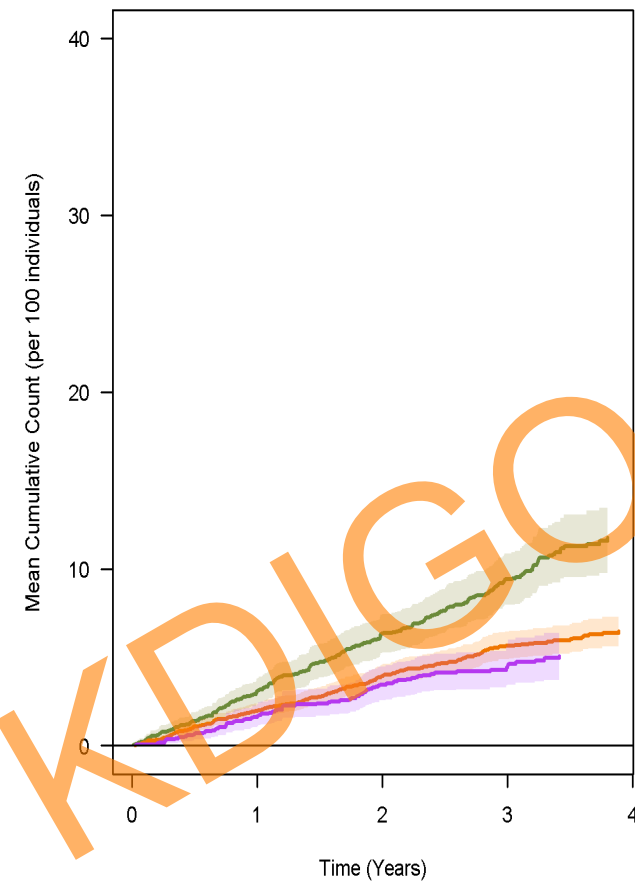
	Intensive N=1,317	Standard N=1,319	p-value
Gait speed (m/s)	0.90 (0.77-1.05)	0.92 (0.77-1.06)	0.375
Gait speed <0.8 m/s	371 (29.7)	369 (29.2)	0.853
Frailty Index	0.18 (0.13-0.23)	0.17 (0.12-0.22)	0.004
Frailty Status			0.013
Fit (FI≤0.10)	159 (12.1)	190 (14.5)	
Less fit (0.10<FI≤0.21)	711 (54.3)	745 (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

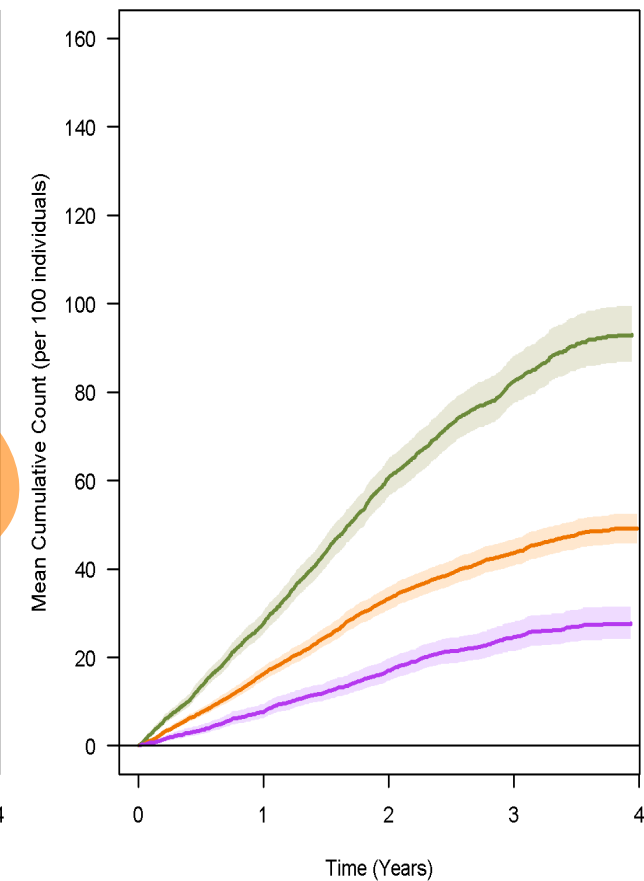
Self-reported falls



Injurious falls



All-cause hospitalizations



Mean Cumulative Count (MCC) Estimates at 3 years (95% CI)

Frailty Status	Self-reported falls	Injurious falls	All-cause hospitalizations
Frail	68.7 (64.1 to 73.5)	9.4 (8.0 to 10.8)	82.6 (77.5 to 88.2)
Less Fit	45.1 (42.2 to 48.0)	5.6 (4.9 to 6.4)	43.5 (40.7 to 46.6)
Fit	35.3 (31.3 to 39.6)	4.4 (3.4 to 5.6)	24.5 (21.4 to 27.9)

MCC estimates are per 100 individuals

Comparisons to Community-dwelling Cohorts

Prevalence of Frailty ($FI > 0.21$)

Age Group	SPRINT	Canadian Community Health Survey
	Proportion (95% CI)	Proportion (95% CI)
65 to 74 years	23.4% (21.9% to 25.0%)	16.0% (15.2% to 16.8%)
75 to 84 years	29.3% (27.4% to 31.2%)	28.6% (27.1% to 30.1%)
85 years or older	41.9% (37.0% to 47.0%)	52.1% (49.2% to 55.0%)

Hoover, et al. *Health Reports* 2013;24(9):10-7

Frailty Status	SPRINT	NHANES 2003-2006
	Proportion	Proportion
Fit ($FI \leq 0.10$)	28.1%	18.8%
Less Fit ($0.10 < FI \leq 0.21$)	37.9%	53.7%
Frail ($FI > 0.21$)	34.0%	27.5%

Blodgett et al. *Arch Gerontol Geriatr* 2015;60(3):464-70.

Research Article

Characterizing Frailty Status in the Systolic Blood Pressure Intervention Trial

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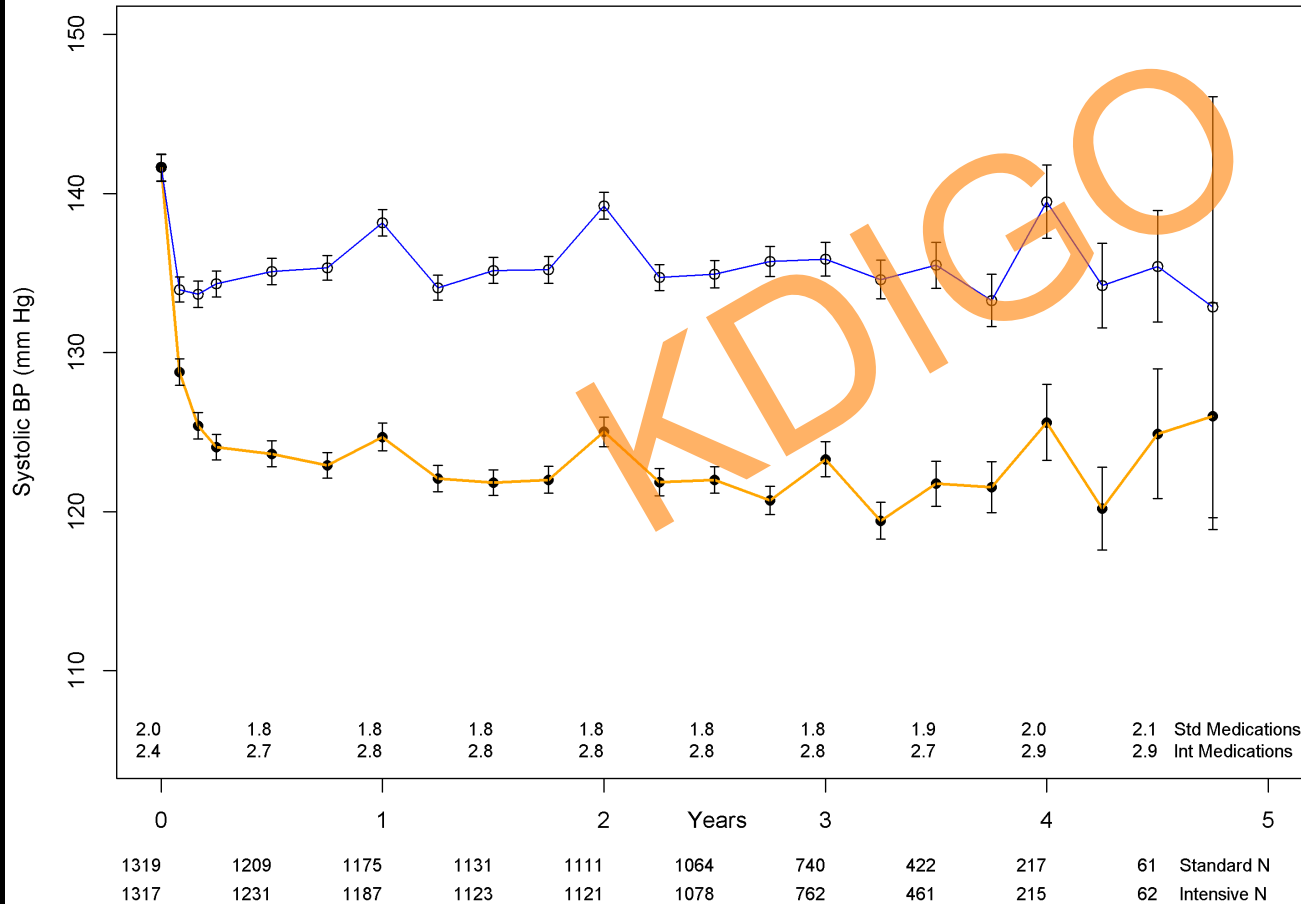
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Systolic BP during Follow-up (75 years and older)



Average SBP
During Follow-up

Standard
135.0 mm Hg
95% CI (134.5, 135.5)

Intensive
123.7 mm Hg
95% CI (123.2, 124.1)

of classes of
antihypertensive meds

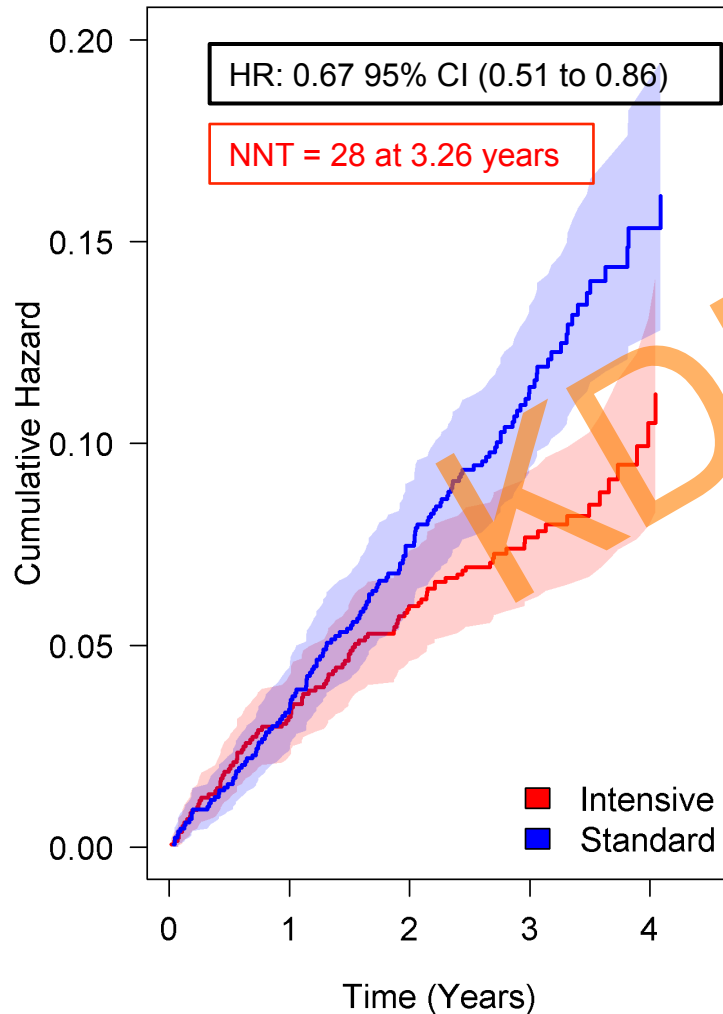
of Participants

Average Blood Pressures during Follow-up by Frailty Status

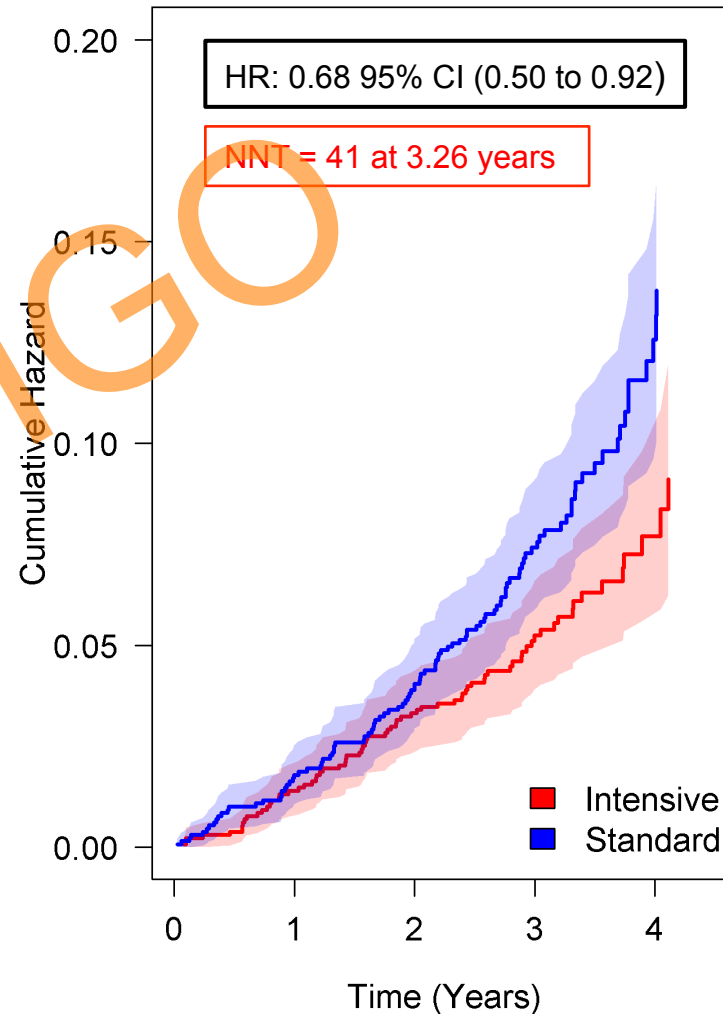
	Frailty Status	Intensive	Standard	Delta
		Mean	Mean	Mean (95% CI)
Systolic BP (mmHg)	Fit	121.5	135.2	13.7 (12.2, 15.2)
	Less fit	123.5	134.8	11.3 (10.6, 12.1)
	Frail	124.5	135.2	10.8 (9.8, 11.8)
Diastolic BP (mmHg)	Fit	62.1	67.7	5.6 (4.4, 6.7)
	Less fit	62.3	67.8	5.5 (4.9, 6.0)
	Frail	62.0	66.4	4.4 (3.6, 5.2)

Cumulative Hazards for SPRINT Primary Outcome and All-Cause Mortality in Participants 75 and older

Primary Outcome

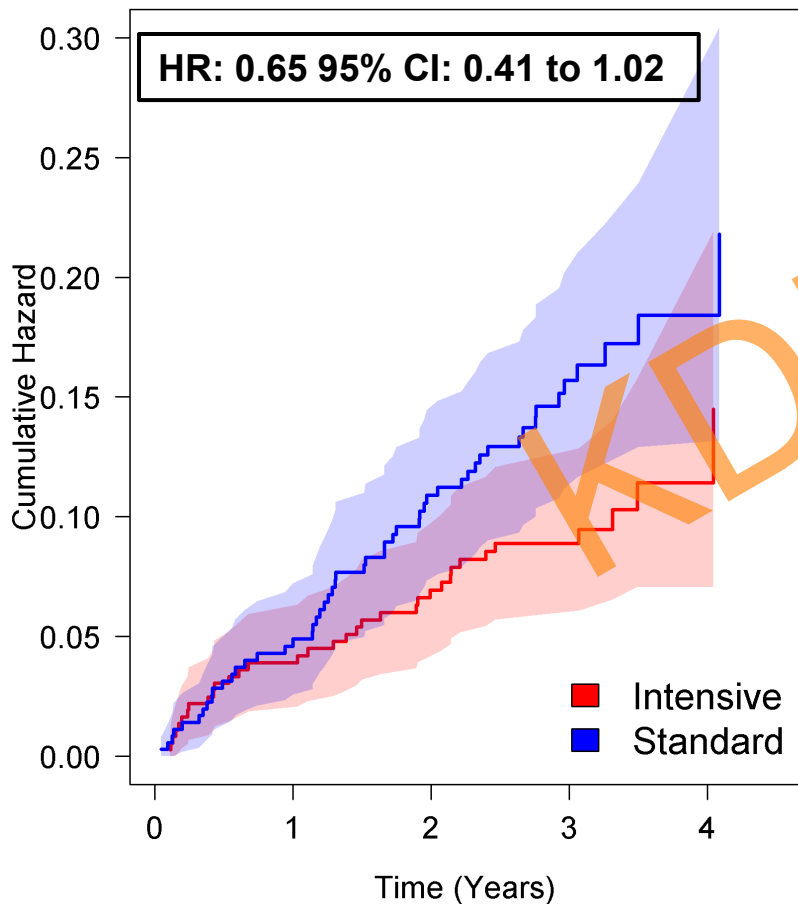


All-Cause Mortality

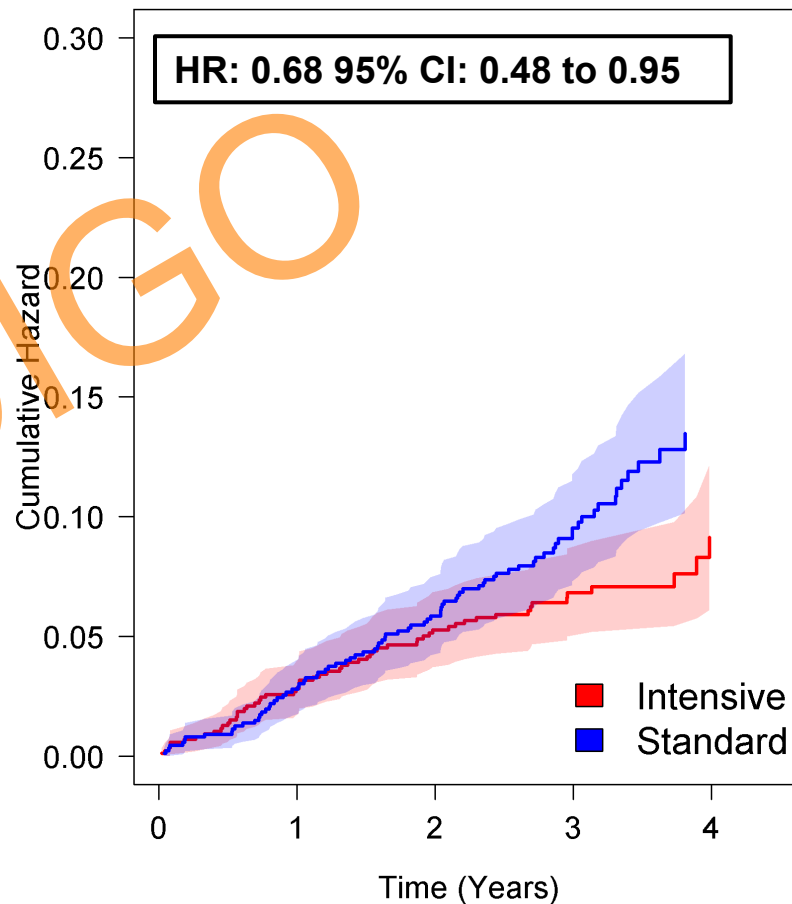


Cumulative Hazards for SPRINT Primary Outcome by Gait Speed

Gait Speed <0.8 m/s (N=740)

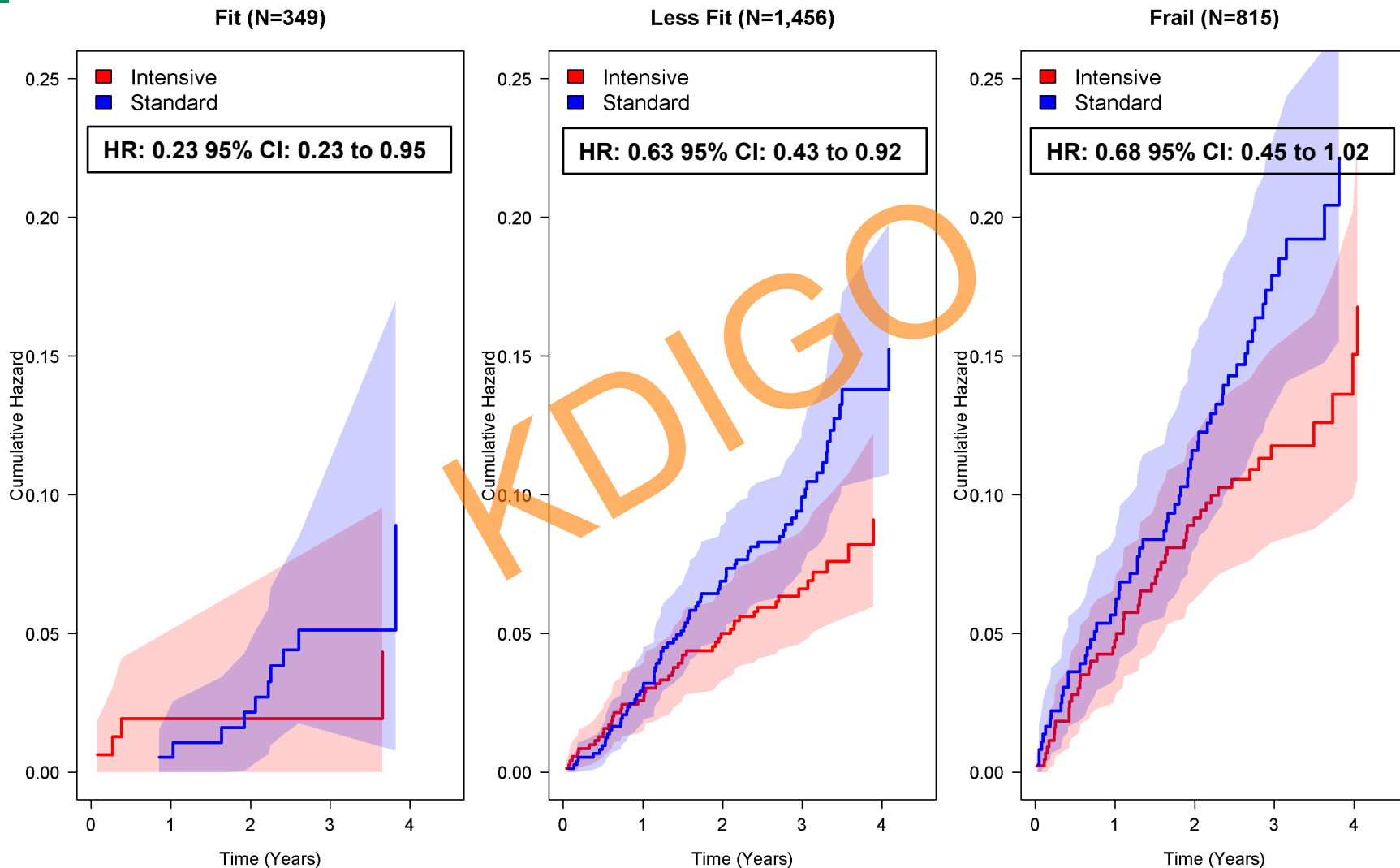


Gait Speed 0.8 m/s or greater (N=1,773)



Interaction p-value = 0.732

Cumulative Hazards for SPRINT Primary Outcome by Frailty Status



Serious Adverse Events (SAE) and Conditions of Interest During Follow-up for Participants 75 Years and Older at Randomization

	Intensive		Standard		HR	p-value
	N	%/yr	N	%/yr		
Serious Adverse Events	640	21.6	638	21.7	1.00	0.931
Conditions of Interest						
Hypotension	36	0.9	24	0.6	1.55	0.098
Syncope	46	1.2	37	1.0	1.25	0.328
Bradycardia	41	1.1	43	1.1	0.90	0.650
Electrolyte abnormality	58	1.5	41	1.1	1.47	0.061
Injurious Fall	70	1.8	79	2.1	0.91	0.575
Acute Kidney Injury	75	2.0	54	1.4	1.40	0.061

N denotes participants with events

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

	Intensive		Standard		HR	p-value
	N	%/yr	N	%/yr		
Sodium<130 mmol/L	66	1.7	44	1.2	1.51	0.034
Sodium>150 mmol/L	1	<0.1	0	-	-	0.290
Potassium<3 mmol/L	17	0.4	11	0.3	1.50	0.303
Potassium>5.5 mmol/L	68	1.8	64	1.7	1.01	0.975
Orthostatic hypotension	277	8.3	288	8.8	0.90	0.242
Orthostatic hypotension with dizziness	25	0.6	17	0.4	1.44	0.252

N denotes participants with events

Orthostatic hypotension defined as drop in systolic BP ≥ 20 mm Hg or drop in diastolic ≥ 10 mm Hg 1 minute after standing. Standing blood pressures were measured at screening, baseline, 1, 6, and 12 months and yearly thereafter. Participants were asked if they felt dizzy at the time the orthostatic measure was taken.

SPRINT Follow-up Experience

	All Participants (75+ years)	
	Intensive	Standard
Consent withdrawn, N (%)	36 (2.7%)	33 (2.5%)
Loss to follow-up, N (%)	26 (2.0%)	31 (2.4%)
Followed but discontinued intervention, N (%)	80 (6.1%)	82 (6.2%)

	Frailty Status					
	Frail		Less Fit		Fit	
	Intensive	Standard	Intensive	Standard	Intensive	Standard
Consent withdrawn, N (%)	15 (3.4%)	10 (2.7%)	17 (2.4%)	16 (2.2%)	1 (0.6%)	3 (1.6%)
Loss to follow-up, N (%)	11 (2.5%)	12 (3.2%)	14 (2.0%)	17 (2.3%)	1 (0.6%)	1 (0.5%)
Followed but discontinued intervention, N (%)	35 (8.0%)	31 (8.3%)	36 (5.1%)	42 (5.6%)	9 (5.7%)	9 (4.7%)

Summary and Conclusions

- For persons age 75+, incidence of primary outcome (composite of CVD events) 33% lower in Intensive compared to Standard Group and all-cause mortality reduced by 32%
- The “number needed to treat” for age 75+ to prevent a primary outcome event or death during a median follow-up of 3.26 years was 28 and 41, respectively
- Benefits of more intensive BP lowering impacted health events that trigger incident disability and were the same for ambulatory frail
- Intensive SPB control is one of the first interventions to show reduction in mortality for ambulatory frail elders

Summary and Conclusions

- SPRINT DOES NOT inform treatment goal for nursing home, Assisted Living, CHF, Diabetes patients but no other common chronic conditions were excluded
- The direction and significance (by HR) of the SAEs were the same for participants 75+ and those < age 75
- The results for dementia and, to some extent, progression of chronic kidney disease in seniors remains unknown pending SPRINT-ASK, an extension of follow-up funded by NIA and NIDDK
- Additional SPRINT follow-up will provide critical evidence on these important outcomes

How shall we then practice?

1. Focus on preserving independence and preventing disability
2. Reduce disability risk with careful titration of BP control
3. Carefully measure blood pressure (seated, quiet 5 minutes)
4. Use as few medications as possible
5. Clinical trials and guidelines are just—guidelines—so individualize care and see if your ambulatory patient can achieve an SBP below 130

What Happened to Mrs S?

- The ring was offered and accepted on New Year's Eve instead of Valentine's day 2015
- Wedding set for June 2015 (of course).
- Mrs. S had a stroke the first week of May and due to complications was not able to make that wedding.
- Would she have been there if I knew then what I know now?

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