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COI Disclosure

Jeff D. Williamson, MD, MHS

- **Funding from the NHLBI, NIDDK, NIA, NINDS, under Contract Numbers HHSN268200900040C, HHSN268200900046C, HHSN268200900047C, HHSN268200900048C, HHSN268200900049C, and Inter-Agency Agreement Number A-HL-13-002-001**
- **Resources and use of facilities through the US Department of Veterans Affairs**
- **The author's institution has also received related research funding from the Alzheimer's Association and from Biogen**

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Goals for this Presentation

- Importance of the relationship between blood pressure control and cognitive decline and dementia
- Recent clues about subgroups that do or do not benefit from blood pressure lowering
- Expanding the population of people whose functional health benefits from better blood pressure control

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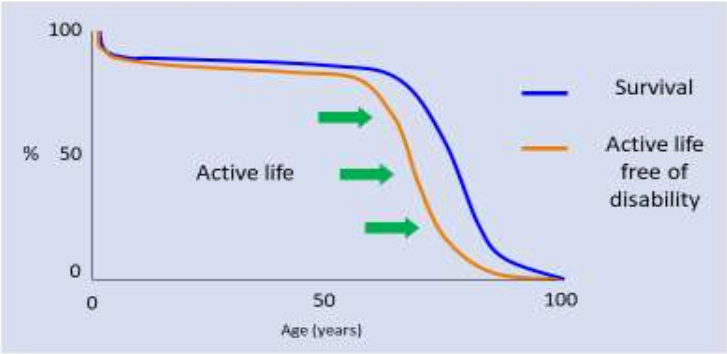
Common Ambulatory Outpatient Practice Scenario

- Mr. E.G. and Mrs. F.G.
- 68 year old mom and grandmother, 6th grade teacher
- 69 year old dad and grandfather. Retired US postal worker
- Together beginning exercise and diet program; concerned about improving fitness
- He is on 2 medications for blood pressure control and a statin.
- She is on statin, metformin (mild hyperglycemia) and 1 medication for BP
- Her mom (also my patient) developed memory loss in her 70s and then dementia; His dad is institutionalized due to CHF and stroke and mild cognitive impairment
- Both want to reduce risk for experiencing their parents' disability.
- Both with blood pressures 135-145 systolic on most office visits
- What is the best evidence for any advice to them about reducing their risk for disability due to cognitive decline?

4

A Primary Focus Geriatric Medicine Clinical Care and Research: To Expand Active Life Expectancy



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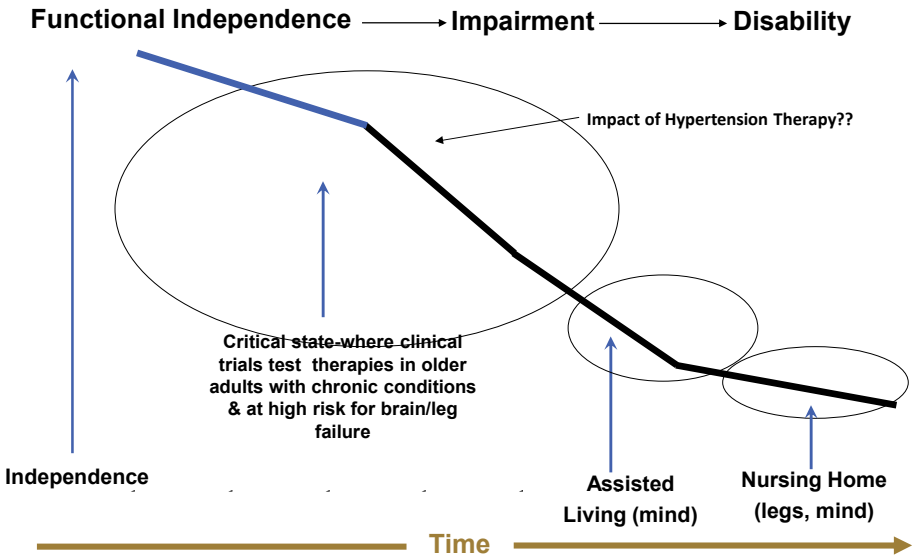
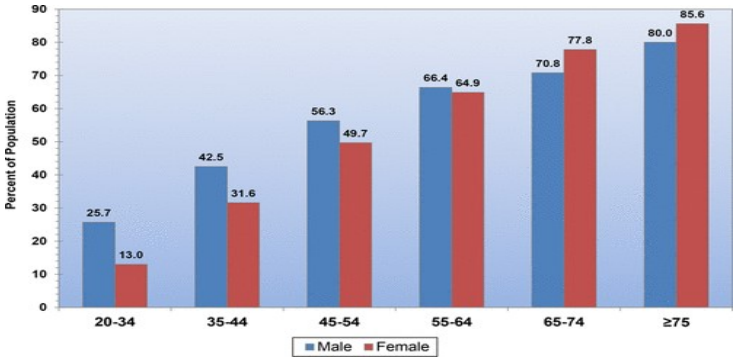
Trajectory of Cognitive Functional Disability



6

Blood Pressure Reduction: A Powerful Public Health Opportunity for Prevention of Age-Related Disability:

Five million US adults ≥ 65 years of age have dementia, a number expected to more than double by 2060.

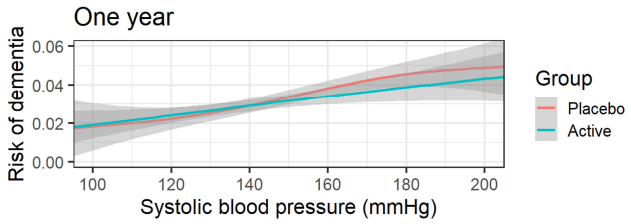


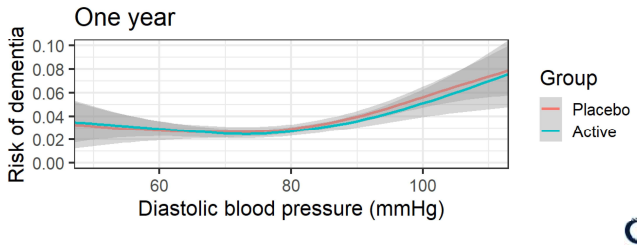
Prevalence of hypertension in adults ≥20 years of age by sex and age (NHANES, 2013–2016)

Benjamin et al, *Circulation*, 2019.

7

"Dementia" Risk Over 4.5 years by Achieved Blood Pressure at 1 Year in HYVET, SYST-EUR, ADVANCE, PROGRESS, SHEP





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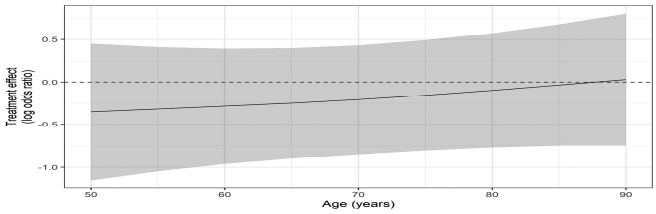
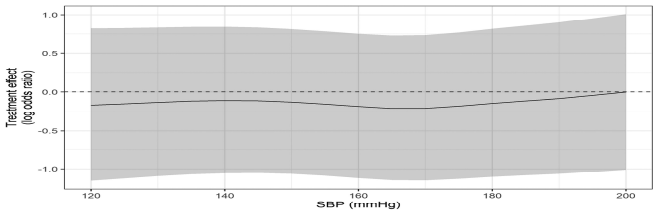
Effect of Antihypertensive Treatment on Risk of Dementia by 1) Age and 2) Baseline Systolic Blood Pressure

(HYVET, SYST-EUR, ADVANCE, PROGRESS, SHEP)



[a]*Adjusted for baseline systolic blood pressure (SBP)*

Relative log odds ratios



[b]*Adjusted for baseline age*

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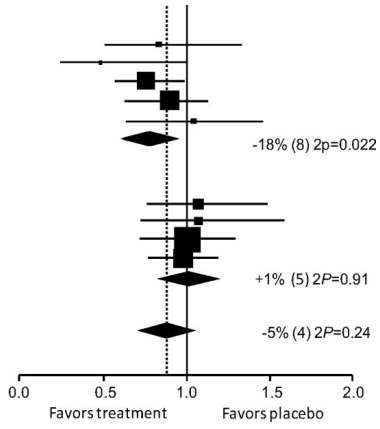
Greater than 10mmHg Blood Pressure Lowering is Necessary to Impact Incidence of Dementia Risk in Placebo-Controlled Clinical Trials

	ΔSBP	FU	Control	Active
SHEP	12.0	4.9	44 / 2371	37 / 2365
Syst-Eur	10.1	2.0	21 / 1180	11 / 1238
PROGRESS/Com	12.8	3.9	136 / 1774	106 / 1770
HYVET-COG	15.0	2.2	137 / 1649	126 / 1687
ADVANCE	5.6	4.3	37 / 5571	39 / 5569
All DIUs/CCBs	9.9	3.5	375 / 12545	319 / 12269
Heterogeneity: Q=3.49, p=0.32				
PROGRESS/Per	4.9	3.9	81 / 1280	87 / 1281
SCOPE	3.2	3.9	57 / 2460	62 / 2477
PRoFESS	3.8	2.5	409 / 8646	408 / 8624
TRANSCEND	4.0	4.7	245 / 2689	239 / 2694
All ACEIs/ARBs	4.1	3.8	792 / 15075	796 / 15076
Heterogeneity: Q=0.49, p=0.92				
All trials	6.6	3.6	1167 / 27620	1115 / 27705
Heterogeneity: Q=7.95, p=0.44				



American Heart Association.

Jan A. Staessen et al. Hypertension. 2011;57:e6-e7

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SPRINT Design

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

Randomized controlled trial of target systolic BP

Intensive Treatment Goal SBP < 120 mm Hg	*Standard Treatment Goal SBP < 140 mm Hg*
N = 4678	N = 4683

- **Major Exclusion Criteria**
  - Stroke (SPS3)
  - Diabetes (ACCORD)
  - Congestive heart failure
  - CKD with eGFR <20 ml/min/1.73 m2
  - Standing BP <110 mm Hg

- **Outcomes**
  - Cardiovascular Disease
  - All-cause mortality
  - Kidney Disease
  - Mild Cognitive Impairment & Dementia

ClinicalTrials.gov (NCT01206062)
Ambrosius *et al. **Clin Trials*** (2014)

Wake Forest Baptist Medical Center

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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)

Wake Forest Baptist Medical Center

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SPRINT

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

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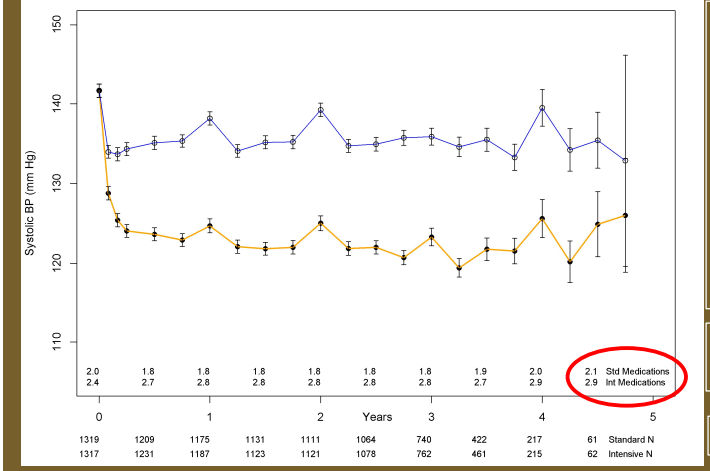
SPRINT

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

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SPRINT
Systolic Blood Pressure Intervention Trial

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

	Intensive		Standard			
	N	%/yr	N	%/yr	HR	p-value
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

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The SPRINT-MIND Neurocognitive Battery

	Components of In-Person Cognitive Screening Battery	Components of In-Person Cognitive Extended Battery	Components of Telephone Cognitive Battery
Global Functioning	Montreal Cognitive Assessment		Modified Telephone Interview for Cognitive Status
Executive Function	Digit Symbol Coding Test		
Speed of Processing		Trail Making Test Parts A and B	Oral Trail Making Test Parts A and B
Learning and Memory	Logical Memory	Hopkins Verbal Learning Test-Revised	
Visual-Spatial Memory		Modified Rey-Osterreith Complex Figure	
Working Memory and Attention		Digit Span Forward and Backward	
Verbal Fluency		Category Fluency-Animals	Category Fluency-Animals
Language and Naming		Boston Naming Test	

- Participants scoring below education and race/ethnicity-specific thresholds on the MoCA were then administered remaining tests, and the **Functional Activities Questionnaire** was administered to a proxy
- Participants that could not complete in-person testing were administered a validated telephone battery. See Rapp *et al. J Am Geriatr Soc* (2012)

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JAMA Network

From: **Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial**
JAMA. Published online January 28, 2019. doi:10.1001/jama.2018.21442

Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

Outcomes	Treatment Group: Intensive No. With Outcome/Person-Years	Intensive Cases per 1000 Person-Years	Standard No. With Outcome/Person-Years	Standard Cases per 1000 Person-Years	Hazard Ratio (95% CI)[a]	*P* Value
Probable dementia	149/20 569	7.2	176/20 378	8.6	0.83 (0.67-1.04)	.10
Mild cognitive impairment[b]	287/19 690	14.6	353/19 281	18.3	0.81 (0.69-0.95)	.007
Composite of mild cognitive impairment or probable dementia	402/19 873	20.2	469/19 488	24.1	0.85 (0.74-0.97)	.01

[a] Intensive treatment group vs standard treatment group based on Cox proportional hazards regression.

[b] Participants adjudicated as having probable dementia at the first follow-up visit (year 2) do not contribute to the analyses of mild cognitive impairment.

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Adjudication of Cognitive Status: A Key SPRINT-MIND Innovation

Probable Dementia, MCI, No Impairment

Screening Cognitive Battery

+

Extended Cognitive Battery

+

Proxy Report (FAQ or Modified Dementia Questionnaire)

+

Depression (PHQ-9) and Medications

=

Expert Adjudication (w/classification: PD, MCI, No Impairment)

Adjudicators were blinded to treatment group and BPs

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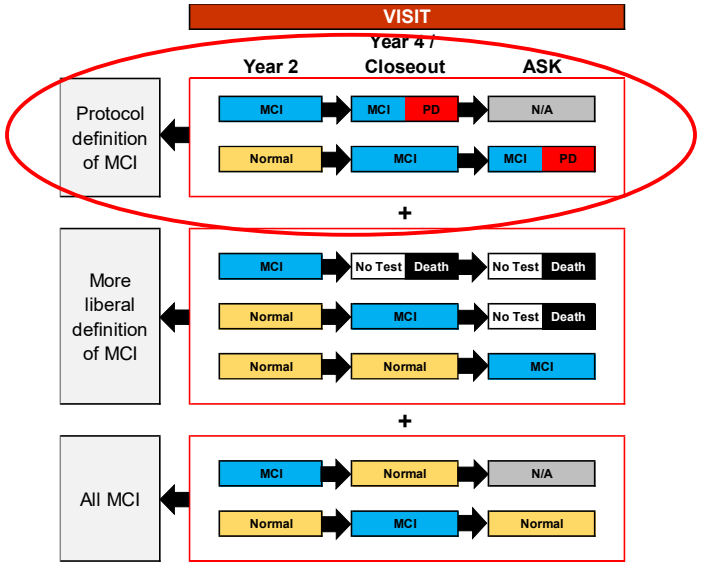
Definitions for Adjudicate Mild Cognitive Impairment (MCI) Outcomes



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Adjudicated MCI in SPRINT is a Much Higher Risk State for Incident Dementia Relative to Normal Cognition

(10X greater)

2 Year Transition Probabilities

Transition		Overall	Intensive Treatment	Standard Treatment
From	To			
Normal Cognition	MCI	4.3% (3.9%, 4.9%)	4.1% (3.6%, 4.6%)	4.6% (4.1%, 5.2%)
Normal Cognition	Probable Dementia	0.6% (0.5%, 0.9%)	0.6% (0.3%, 0.9%)	0.6% (0.5%, 0.9%)
Normal Cognition	Death	2.3% (2.0%, 2.7%)	2.2% (1.9%, 2.7%)	2.4% (2.0%, 2.9%)
MCI	Intermittent MCI	31.6% (28.9%, 34.5%)	32.8% (29.2%, 36.4%)	30.5% (27.2%, 34.0%)
MCI	Probable Dementia	5.9% (4.5%, 7.7%)	4.9% (3.4%, 7.0%)	6.9% (5.0%, 9.5%)
MCI	Death	10.0 % (8.3%, 11.9%)	9.3% (7.1%, 12.1%)	10.5% (8.3%, 13.3%)

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Primary MRI results

MRI Structural Outcome	**Intensive Treatment** Change (95% CI)	**Standard Treatment** Change (95% CI)	Difference in Change (95% CI)	P Value
Transformed WML Volume, asinh(cm^3)	0.15 (0.11, 0.19)	0.28 (0.24, 0.33)	-0.13 (-0.19, -0.07)	<0.001
WML Volume, cm^3 (RLMM)	0.92 (0.69, 1.14)	1.45 (1.21, 1.70)	-0.54 (-0.87, -0.20)	-
Total Brain Volume, cm^3	-30.6 (-32.3, -28.8)	-26.9 (-28.8, -24.9)	-3.7 (-6.3, -1.1)	0.006

For change estimates, negative values denote decreases from baseline, while positive values indicate increases from baseline. Difference in Change represents intensive treatment group minus standard treatment group. SE denotes Standard Error, CI confidence interval, WML white matter lesion, and RLMM robust linear mixed model.

JAMA Network

From: **Association of Intensive vs Standard Blood Pressure Control With Cerebral Blood Flow: Secondary Analysis of the SPRINT MIND Randomized Clinical Trial**

JAMA Neurol. Published online March 07, 2022. doi:10.1001/jamaneurol.2022.0074

Table 2. Changes in Cerebral Blood Flow by Treatment Group

	Cerebral blood flow, (95% CI), mL/100 g/min[a]							
	Intensive treatment			Standard treatment				
Outcome	Baseline	Follow-up	Change	Baseline	Follow-up	Change	Difference in change (95% CI)	*P* value
Whole brain	38.90 (36.64 to 41.17)	40.36 (37.95 to 42.77)	1.46 (0.08 to 2.83)	37.96 (35.67 to 40.26)	37.12 (34.66 to 39.58)	-0.84 (-2.30 to 0.61)	2.30 (0.30 to 4.30)	.02
Gray matter	50.76 (47.01 to 54.52)	52.91 (49.01 to 56.80)	2.14 (0.41 to 3.87)	49.40 (45.61 to 53.19)	49.06 (45.11 to 53.00)	-0.34 (-2.17 to 1.48)	2.49 (-0.03 to 5.00)	.05
White matter	19.86 (18.85 to 20.88)	20.51 (19.35 to 21.67)	0.65 (-0.32 to 1.61)	19.41 (18.36 to 20.46)	18.57 (17.36 to 19.79)	-0.83 (-1.85 to 0.18)	1.48 (0.08 to 2.88)	.04
Periventricular white matter	15.79 (14.81 to 16.78)	16.11 (15.01 to 17.21)	0.32 (-0.54 to 1.17)	15.48 (14.47 to 16.50)	14.60 (13.45 to 15.76)	-0.88 (-1.80 to 0.04)	1.20 (-0.06 to 2.45)	.06

[a] Estimates based on a linear mixed model, adjusting for age, sex, and days since randomization, with random effects for participant and magnetic resonance imaging facility. Estimates represent least-square means, with follow-up estimates computed at 1452 days (4.0 years) postrandomization, which was the median follow-up in both treatment groups. For change estimates, negative values denote decreases from baseline, while positive values indicate increases from baseline. Difference in change represents intensive treatment group minus standard treatment.

Table Title:

Changes in Cerebral Blood Flow by Treatment Group[a] Estimates based on a linear mixed model, adjusting for age, sex, and days since randomization, with random effects for participant and magnetic resonance imaging facility. Estimates represent least-square means, with follow-up estimates computed at 1452 days (4.0 years) postrandomization, which was the median follow-up in both treatment groups. For change estimates, negative values denote decreases from baseline, while positive values indicate increases from baseline. Difference in change represents intensive treatment group minus standard treatment.

Blood Pressure Lowering Not Only Benefits the Middle Aged

Outcome	Subgroup	Intensive Treatment Events / No.	Intensive Treatment Cases / 1000 Person-Years	Standard Treatment Events / No.	Standard Treatment Cases / 1000 Person-Years	Hazard Ratio (95% CI)	P value
PD	<75 years	54 / 3085	3.54	60 / 3087	3.97	0.90 (0.62, 1.30)	0.57
	≥75 years	95 / 1193	17.83	116 / 1198	22.04	0.88 (0.66, 1.16)	0.37
	≥80 years	63 / 524	28.59	65 / 513	30.51	1.02 (0.71, 1.47)	0.92
MCI	<75 years	125 / 3085	8.42	172 / 3087	11.77	0.74 (0.58, 0.93)	0.01
	≥75 years	162 / 1193	33.47	181 / 1198	38.78	0.89 (0.72, 1.11)	0.29
	≥80 years	73 / 524	37.03	95 / 513	52.31	0.70 (0.51, 0.96)	0.03
MCI+PD	<75 years	168 / 3085	11.27	210 / 3087	14.32	0.80 (0.65, 0.98)	0.04
	≥75 years	234 / 1193	47.11	259 / 1198	53.7	0.91 (0.76, 1.09)	0.30
	≥80 years	122 / 524	59.55	139 / 513	73.01	0.82 (0.63, 1.06)	0.13

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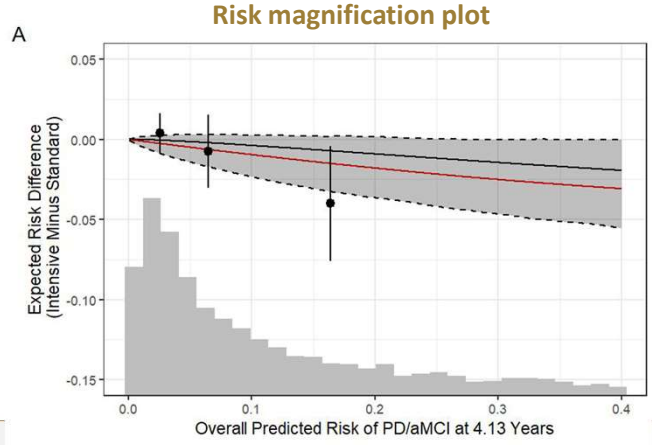
Cognitive benefit of intensive SBP control grows linearly as baseline risk of future MCI or dementia grows

Risk magnification plot



Factors associated with cognitive risk:

Higher:
Older age,
Enrolled in Medicare
VA insurance
Higher baseline serum creatinine

Lower:
Higher MoCA
Being employed

Ghazi L, Bress A, Williamson et.al. JAMA Open 2023

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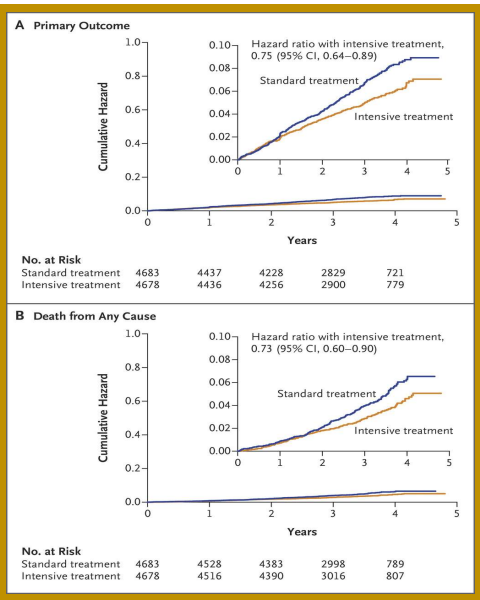
Primary Outcome and Death from Any Cause



During Trial: Number Needed to Treat (NNT) to prevent a primary outcome in one participant = 61

During Trial: Number Needed to Treat (NNT) to prevent death in one participant = 90

The SPRINT Research Group. N Engl J Med 2015. DOI: 10.1056/NEJMoa1511939

The NEW ENGLAND JOURNAL of MEDICINE

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SPRINT MIND 2020

Funding from Alzheimer's Association and NIA

- Continued assessment of the SPRINT MIND participants for dementia incidence
-
- Final assessments by January 2024
- Anticipated results AAIC in 2024

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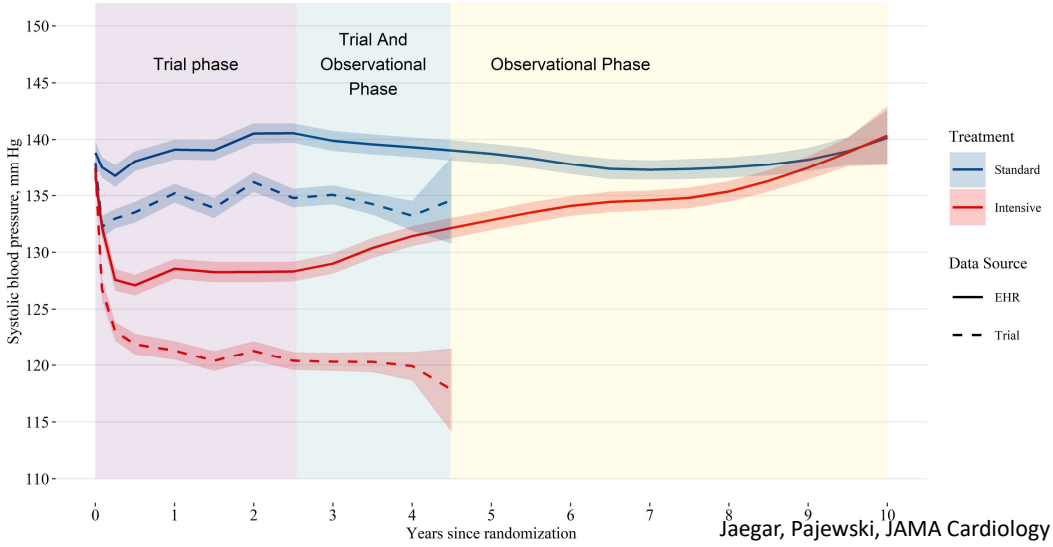
Benefit of blood pressure lowering wanes quickly when stopped……



Jaegar, Pajewski, JAMA Cardiology Nov 2022

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IMPACTS-MIND Trial (Tulane)

Katherine Mills, Jiang He, Marie Krousel-Wood, Erin Peacock, Jing Chen, Jeff Williamson, Paul K. Whelton

10 Primary Care Organizations in Louisiana and Mississippi

36 Clinics
(1260 Study Participants)

Multicomponent Intervention
18 Clinics
(35 participants per clinics)

Enhanced Usual Care
18 Clinics
(35 participants per clinics)

Average of 42 Months
Intervention and Follow-up

Difference in Mean Change in Cognitive Score from Baseline to 42 Months

<u>Overall Objective</u>
to test a multifaceted strategy for implementing an intensive BP intervention protocol adapted from SPRINT targeting systolic BP <120 mmHg on cognitive decline in racial minority and low-income hypertensive patients in primary care

<u>Participants</u>

- Men or women 40+ years old (with 2/3s 60+)
- Baseline systolic BP ≥140 mm Hg if no BP meds or ≥130 mm Hg if BP meds
- Patients at included clinics
- No baseline dementia

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IMPACTS MIND Baseline characteristics (N=819)

Montreal Cognitive Assessment (MoCA), mean (SD)		19.9 (4.5)
Age, mean years (SD)		60.4 (9.0)
Black, %		65.9
Female, %		59.6
Education, %	< High school graduate High school graduate > High school	26.8 30.4 42.8
Annual household income, %	 < $10,000 $10,000 - <$25,000 $25,000 - <$50,000 ≥ $50,000	 24.7 45.8 21.1 8.4
Self-reported history of diabetes, %		41.3
Self-reported history of depression, %		27.5
BMI, Mean (SD)		33.6 (9.4)

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Summary

- **Intensive BP control reduces the risk for disabling acute and chronic conditions such as CHF, stroke, MI and the combined incidence of MCI or dementia, even in older adults**
- **Persons with early or increased risk for memory impairment appear to benefit most from intensive BP control in the first 5 years**
- **However, older adults with intact cognitive function more likely than persons with early cognitive impairment to experience CVD and mortality benefit from intensive BP control**
- **Definitive trials are needed on pragmatic implementation of blood pressure control in diverse populations**

Wake Forest University School of Medicine | The academic core of Atrium Health

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Acknowledgments

- **9,361 volunteers who agreed to participate in SPRINT**
- Investigators and staff, including SPRINT 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 Institute on Aging (NIA)
  - National Heart, Lung, and Blood Institute (NHLBI)
  - National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
  - National Institute of Neurological Disorders and Stroke (NINDS)
- SPRINT Data and Safety Monitoring Board (DSMB) Takeda and Arbor Pharmaceuticals (donated 5% of medication used)

SPRINT MIND Investigators

Chair: Jeff Williamson, MD, MHS*
Vice Chair: Virginia Wadley, PhD*
MIND Project Manager: Nancy Woolard
MIND Adjudication Manager: Jennifer Walker

SPRINT CC Principal Investigator: **David Reboussin, PhD**
SPRINT Steering Committee Chair: **Paul Whelton, MD, MSc**
SPRINT-MIND Lead Statistician **Nicholas Pajewski, PhD**
SPRINT Project ManagerLetitia Perdue

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Gordon Chelune, PhD*
Jo Cleveland, MD*
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Alan Lerner, MD*
Paula Ogrocki PhD*
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Thank You

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