

Alzheimer's Disease and Related Dementias: Update on diagnosis, treatment and prevention

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SPRINT
Systolic Blood Pressure Intervention Trial

Wake Forest®
School of Medicine

The SPRINT MIND Investigators for the SPRINT Research Group. *JAMA.* 2019;321(6):553-561.

dementia: A primer

MAJOR NEUROCOGNITIVE DISORDER (aka DEMENTIA)

- Evidence of significant cognitive decline from a previous level of performance in two or more of the following domains:
  - Learning/memory, language, executive functions, perceptual motor, social cognition/behavior, or visuospatial abilities
- Cognitive impairments interfere with independence in everyday activities/daily life
- Exclude other psychiatric and neurological explanations (including delirium, depressive disorder etc.)

DSM-5 (2013)
ICD-10 = R41.9

Mild Cognitive Impairment

The Emerging Importance of Mild Cognitive Impairment (MCI)

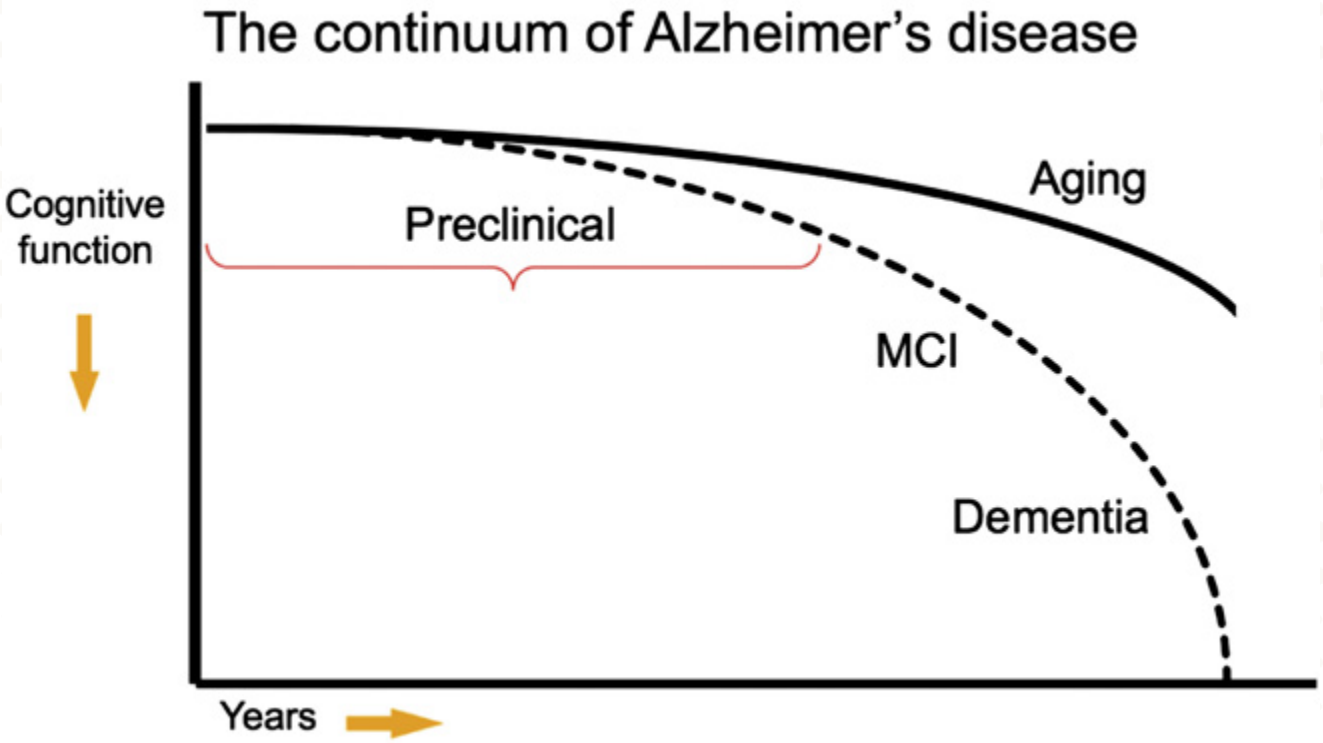
- **Not** normal age-related change
- **Identified in 2004 as a preclinical phase of ADRD**
- **Now a clinical target for prevention & treatment**
- **Is a billable diagnosis with and ICD code: G31.84**
- **Is an unstable clinical state (unlike dementia):**
  - **20-30% of initial MCI reverts to no impairment**
  - **80% of MCI transitions to dementia 5-7 years**
  - **Those that revert to NI still have higher risk for later MCI and ADRD**

Petersen RC *Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183–194.*
Petersen RC, *Mild cognitive impairment as a clinical entity and treatment target. Arch Neurol 2005;62:1160–1163.*
Vega JN, *Mild cognitive impairment: diagnosis, longitudinal course, and emerging treatments. Curr Psychiatry Rep 2014;16:490.*
Roberts R, *Classification and epidemiology of MCI. Clin Geriatr Med 2013;29:753–772.*

Criteria for Diagnosing MCI

- Concern regarding a change in cognition from the patient, knowledgeable informant, or from a skilled clinician observing the patient
- Objective evidence of impairment (from cognitive testing) in 1 or more cognitive domains including memory, executive function, attention, language, or visuospatial skills
- Preservation of independence in functional abilities (although individuals may be less efficient and make more errors at performing activities of daily living and instrumental activities of daily living than in the past)
- No evidence of a major impairment in social or occupational functioning (i.e., not demented)

Normal Cognitive Aging vs ADRD



Sperling et al., 2011

Alzheimer's disease and Related Dementias (ADRD)

- Alzheimer's pathology present in 60-80% of all dementias
  - More prevalent in women
  - Exclusively prevalent in only 10-20% and this is mostly in younger cases

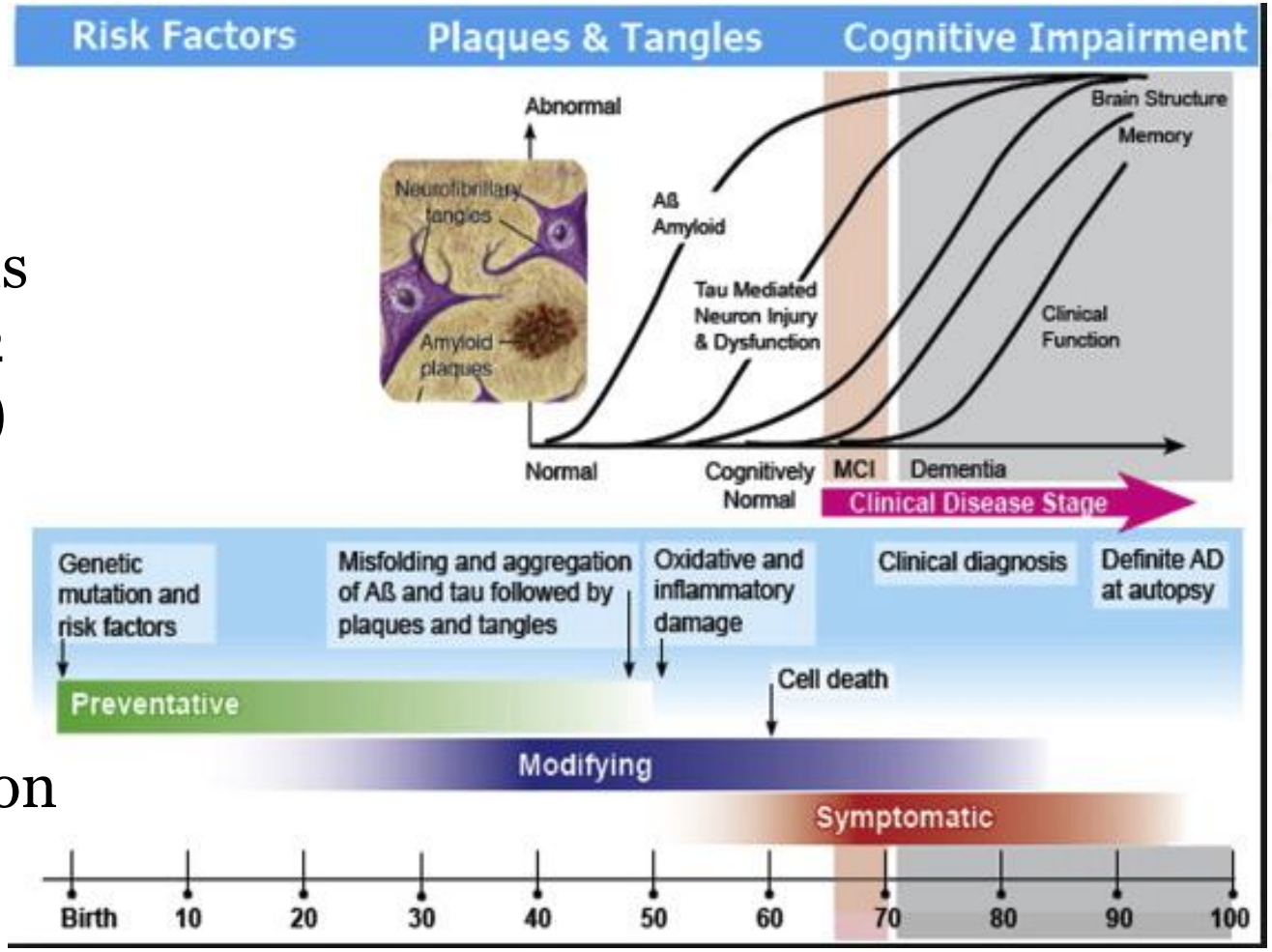
- ADRD 5th leading cause of death in Americans > 65, with rates rising
  - Stroke, heart disease, and prostate cancer deaths decreasing

- ~5.5 million Americans with ADRD in 2010; by 2050 prevalence rises to XY million

Alzheimer's Association, 2019

Genetic & Neuropathological features of AD

- Genetic mutations
  - APP, PS1, PS2
  - EO (Minority)
- APOE 4
  - LO (Majority)
- Beta Amyloid
- Tau
- Neurodegeneration



Trojanowski et al., 2010

Alzheimer's Disease: Clinical features

- Risk factors:
  - age < 70 more likely AD
  - family history (5% autosomal dominant – EO; ~25% cumulative risk LOAD in 1st degree relatives)
  - APOE ε4
  - cardiovascular health status
  - diabetes
  - low educational attainment
  - AA/Hispanic ?
  - Past TBI AD vs ADRD?

Alzheimer's Disease: Clinical features

- Core features:
  - Insidious onset
  - Clear cognitive decline from premorbid level
  - First and most prominent cognitive impairments in Memory/learning, although Non-amnestic presentations exist (language, spatial, executive; PCA; LPA)
- Absent features:
  - Significant vascular burden such as stroke
  - Features of LBD, PPA, FTD or other neurological condition or medication effect

McKhann et al., 2011

Cognitive & behavioral features of Alzheimer's Disease

- Dominant early learning difficulties and memory loss, (e.g., rapid forgetting of new information)
- Relative sparing of remote memories
- Word-finding difficulties (anomia)
- Apraxia
- Can show visuospatial deficits
- Behavioral changes (depression can be common early) and reductions in insight

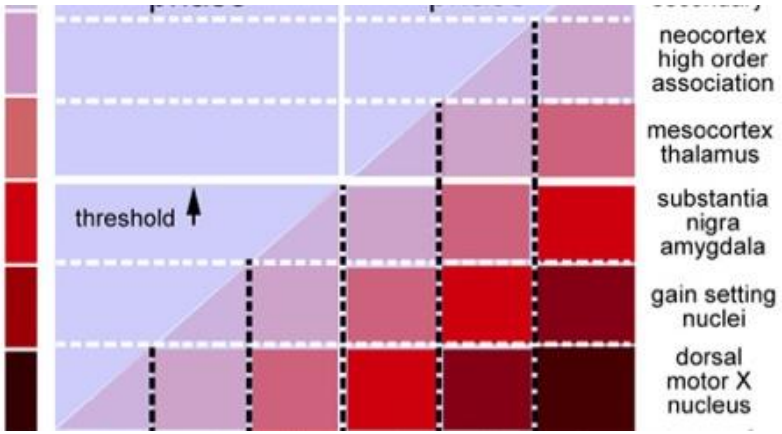
Parkinson's Disease Dementia & Dementia with Lewy Bodies

Parkinson's Disease & Cognition

- Cognitive (non-motor features) are common in PD
  - This does not indicate dementia will occur
- ~1/3 patients have some subtle cognitive findings on NP testing at time of initial diagnosis
- MCI prevalent in PD
- May develop into dementia

Parkinson's Disease Dementia (PDD)

- **Dementia in the context of known Parkinson's disease typically occurs many years (even decades) after motor symptoms arise/diagnosis is made**
- **More common in older PD patients than those with younger onset**
- **Alpha-Synuclein protein –**
  - **major constituent of Lewy bodies & Lewy Neurites in DLB & PPD**
- **Attributable to primary involvement of subcortical structures, but eventually cortex is involved as well**



Braak et al., 2004

Dementia with Lewy bodies (DLB)

- Central Features
  - Dementia
  - Deficits on tests of attention, executive function, and visuospatial ability
    - Prominent memory impairment not found in early stages but is usually evident with progression
- Core Features
  - Fluctuating cognition and/or alertness
  - Visual hallucinations/ misperceptions
  - Parkinsonism
- Suggestive Features
  - REM sleep behavior disorder
  - Severe neuroleptic sensitivity
- Supportive Features
  - Severe autonomic dysfunction
  - Repeated falls and syncope
  - Transient LOA
  - Hallucinations in other modalities
  - Depression

McKeith et al. (2005)

Lewy Body Dementia

Cognitive Deficits

- Substantial attention deficits and prominent executive difficulties
- Visuospatial difficulties & visual misperceptions
- Slowed verbal fluency & processing speed

Preserved Cognitive Domains

- **Confrontation naming**
- **Short- and medium term recall as well as recognition memory**

Dementia with Lewy Bodies vs. Parkinson's Disease Dementia

- Many overlapping cognitive symptoms and clinical symptoms.
  - Frontal-subcortical dysfunction
  - Hallucinations, sleep disturbance, can also occur in non-LB dementia because of medication side-effects, etc.

- **DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism and PDD should be used to describe dementia that occurs in the context of well-established PD (can be many years later)**

- **A 1-year rule between onset of dementia and parkinsonism should be used**

McKeith et al. (2005)

Frontotemporal dementia

Frontotemporal lobar degeneration (FTLD)

- **Encompasses two major substrates, primarily the frontal or temporal cortex, and in some patients asymmetrically**

- **Characterized by three separate syndromes:**
  - **FTD, PPA, SD**

  - **Presenile onset (<65), mean age of onset in 50's**

  - **+ History in 1st degree relative**

Neary et al. (1998)

FRONTOTEMPORAL LOBAR DEGENERATION-BV

- Core Features
  - Insidious onset
  - **Impairment in social and interpersonal conduct**
  - **Emotional blunting**
  - **Loss of insight**

- Supportive Features
  - Behavioral: **Change in hygiene**, distractibility, mental rigidity, hyperorality, perseveration/stereotypy, utilization behavior, **disinhibition**
  - Speech: Economy of speech, pressed speech, stereotypy, echolalia, perseveration, mutism
  - Physical: Reflexes, incontinence, akinesia, akithisia, labile BP
  - **Imaging: Atrophy of frontal/anterior TL structures; can be asymmetric**

Neary et al., 1998

FRONTOTEMPORAL DEMENTIA-BV

Cognitive Deficits

- Attention
- Abstraction
- **Planning**
- **Problem solving**
- Mental flexibility

- Cognitive symptoms can be relatively mild; more prominent behavioral symptoms

Preserved Cognitive Domains

- **Language**
- **Perception**
- **Spatial Functions**
- **Orientation**
- **Not amnestic; however, memory is inefficient and can be impaired secondary to executive dysfunction**

Neary et al., 1998

PROGRESSIVE NON-FLUENT APHASIA

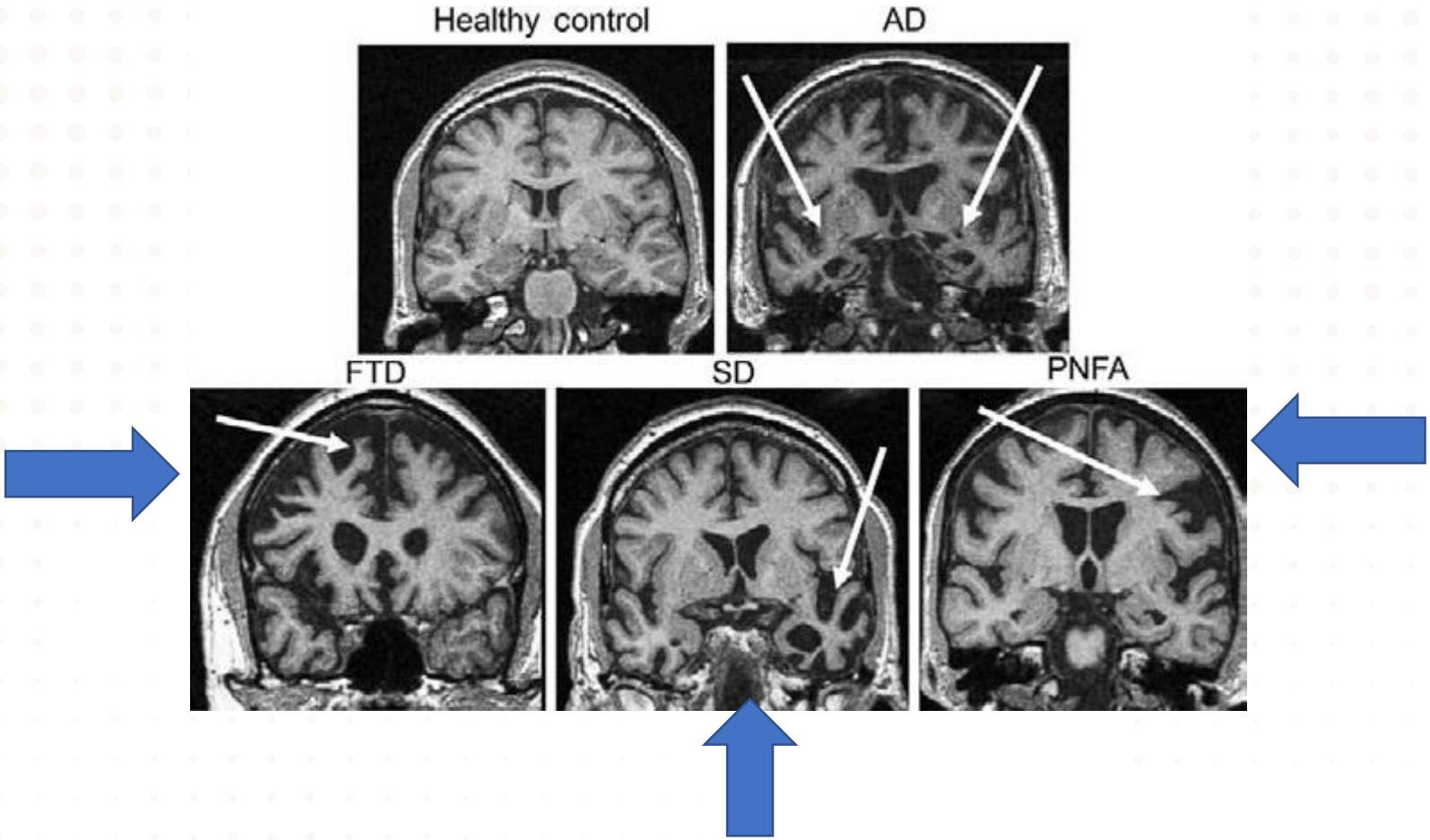
- Core Features
  - Insidious onset & gradual progression
  - Nonfluent (e.g., halting, effortful) spontaneous speech with at least 1 of:
    - Agrammatism, phonemic paraphasias, anomia

The b,boy fly, flying a kite. The t … dog and maybe the kite might come back down here and maybe the dog to try and catch it and these people on the /se/, sailboat … Then I don't know what there, there … There's a /banket/ in /spe/ and a bucket … a … a … shes p … p … pouring coke for a … a … um … like the …

- Supportive Features
  - Speech: Oral apraxia, impaired repetition, alexia/agraphia, be impaired) early preservation of single word meaning (comprehension of complex passages may
  - Behavior: Preserved social skills early (late behavioral change)
  - Physical: late contralateral primitive reflexes, akinesia, rigidity, tremor
  - Imaging: L posterior frontal-insular atrophy

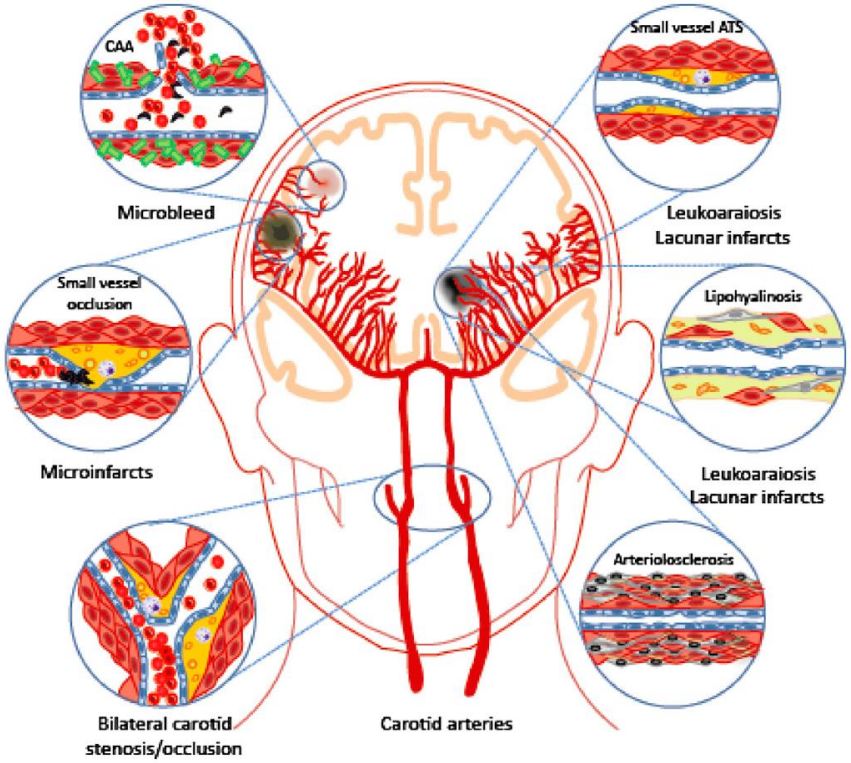
Mesulam et al., 1982; Neary et al., 1998; Miller & Boeve, 2013

Neuroimaging features



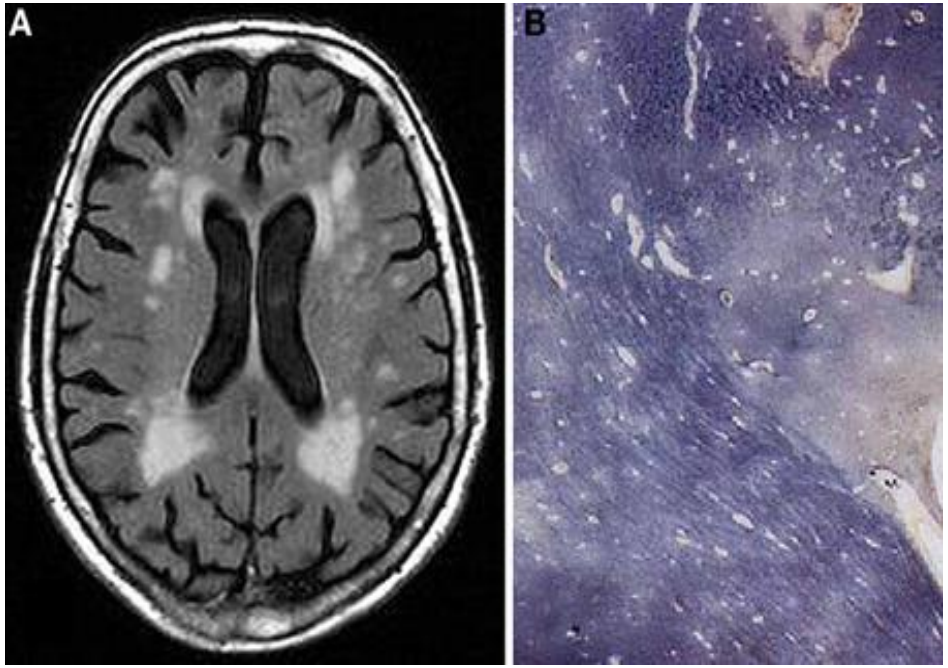
Vascular Cognitive Impairment and Dementia (present in 80% 0f cases over age 70)

Diverse small vessel disease pathways hypothesized to produce a variety of VCID tissue injury mechanisms



Radiologic Features of VCID

White matter degeneration is a pathologic process commonly seen in persons with high vascular disease burden and strongly associated with cognitive impairment



Jellinger et al. Frontiers in Aging Neuroscience, 2013

Gaps in knowledge:
Translational animal models of WMH informed by clinical research.

Differences in tissue and small vessel dysfunction between gray and white matter.

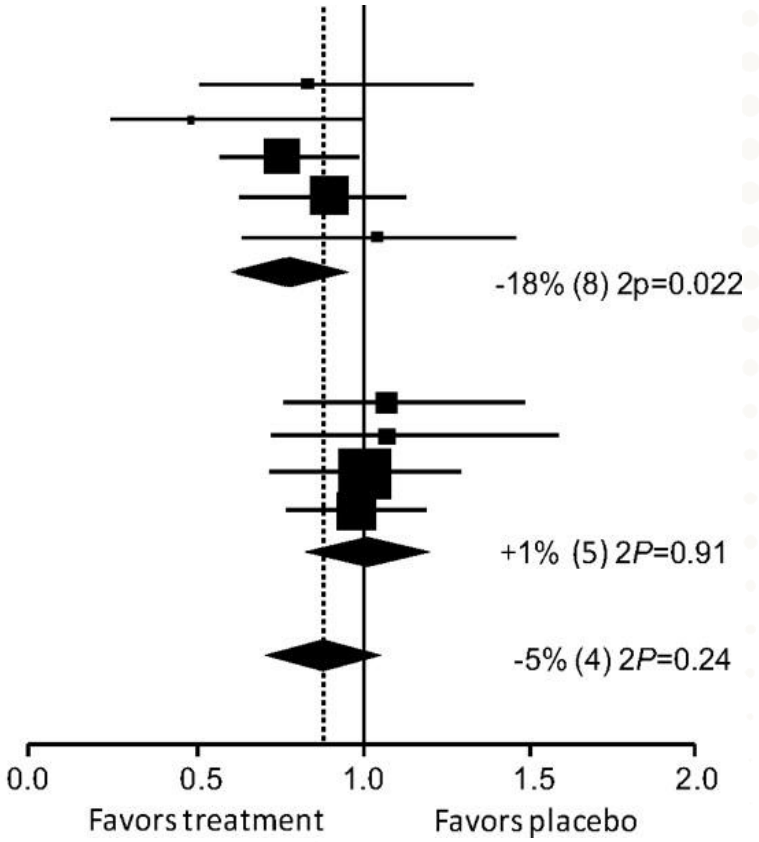
Window of therapeutic opportunity vascular and axonal rescue?

Prevention of Dementia: What the evidence?

- Blood ressure control
- Physical Exercise
- Diet
- Brain Exercise
- Statins

Effects of Blood Pressure Lowering on the Incidence of Dementia 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				



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

American Heart Association.

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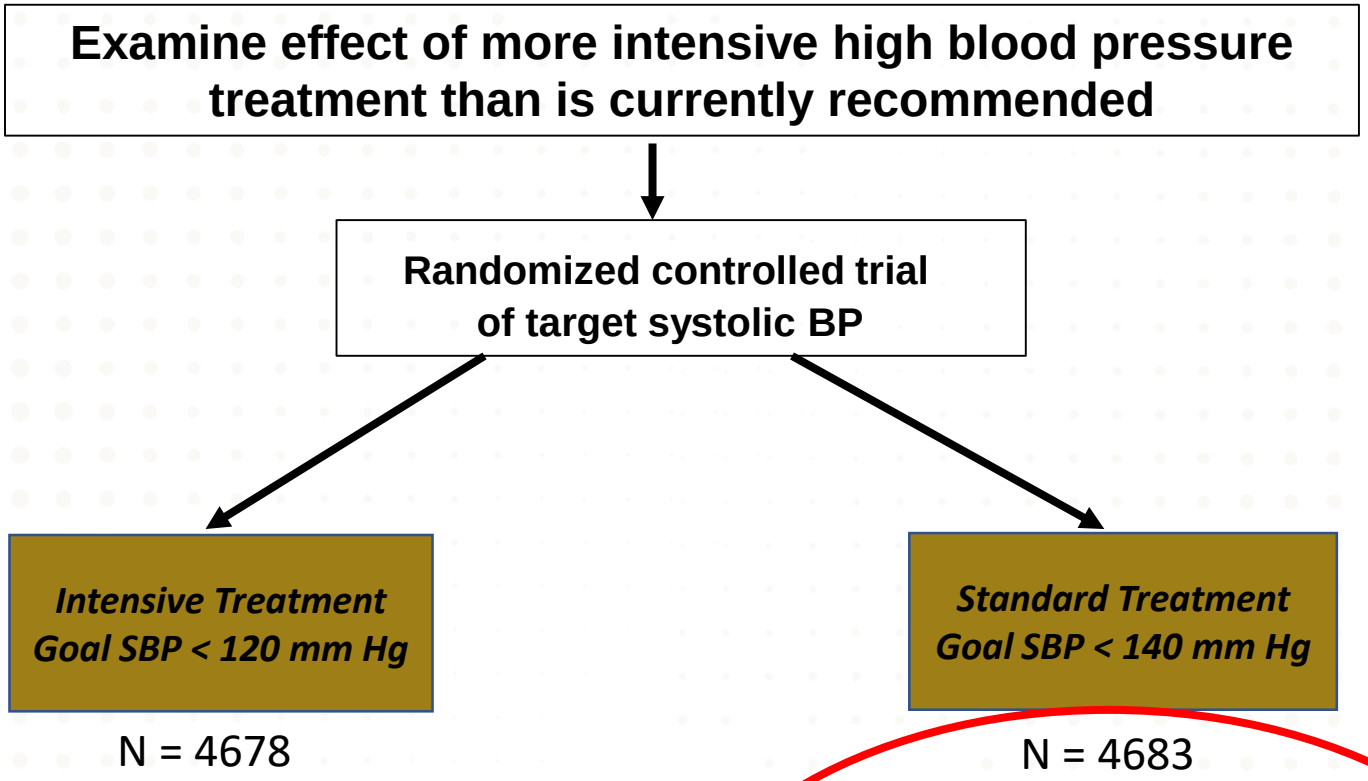
RCT Evidence for BP Lowering and Cognitive Function / Dementia

Study	Total N	Outcome	Follow-up
AVEC Trial (2012)	53	Cognitive Function	1 years
ONTARGET (2011)	25,620	Cognitive Function	4.7 years
TRANSCEND Trial (2011)	5,926	Cognitive Function	4.7 years
PRoFESS Trial (2008)	20,332	Cognitive Function	2.4 years
HYVET-COG (2008)	3,336	Dementia	2.2 years
PROBE Study (2006)	160	Cognitive Function	24 weeks
SCOPE (2005)	4,937	Dementia	3.7 years
PROBE Study (2004)	144	Cognitive Function	16 weeks
PROGRESS (2003)	6,105	Dementia / Cognitive Function	3.9 years
Sys-Eur Trial (1998)	2,418	Dementia	2.0 years
MRC Treatment Trial of Hypertension in Older Adults (1996)	2,584	Cognitive Function	4.5 years
HOPE Study (1996)	81	Cognitive Function	24 weeks
SHEP Study (1994)	4,736	Cognitive Function	5 years
Croog *et al.* (1994)	309	Cognitive Function	22 weeks
Croog *et al.* (1986)	626	Cognitive Function	24 weeks

- Only 4 trials assessed dementia as an outcome; none adjudicated; limited batteries
- **Of those 4 trials, only 2 had a duration greater than 3 years**
- **No trials assessed mild cognitive impairment (MCI) as an outcome**
- Also vastly different starting BP levels and deltas across studies

Adapted from Elias *et al.* ***Am J Hypertens*** (2018)

SPRINT Design



- **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)

Major Inclusion Criteria

- ≥ 50 years old
- Systolic blood pressure: 130 – 180 mmHg (treated or untreated)
- Additional cardiovascular disease (CVD) risk
  - Clinical or subclinical CVD (excluding stroke)
  - Chronic kidney disease (CKD), defined as eGFR 20 – < 60 ml/min/1.73m^2
  - Framingham Risk Score for 10-year CVD risk ≥ 15%
  - Age ≥ 75 years

At least one

Baseline Characteristics: Heterogeneity

	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 Heterogeneity Participants 75 years or older: Enriched with persons likely to

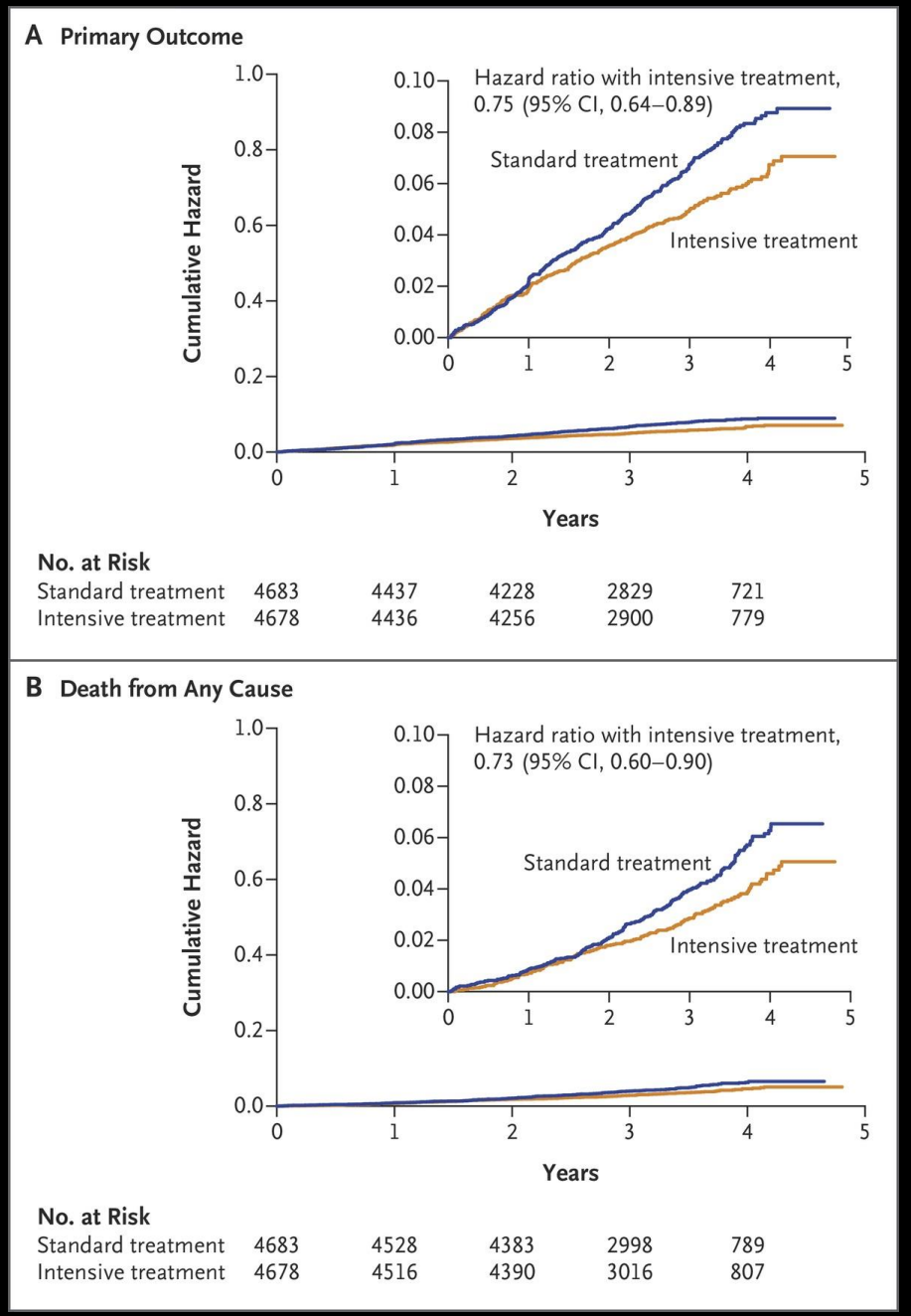
	Intensive N=1,317	Standard N=1,319	p-value
Gait speed (m/s)	0.90 (0.77-1.05)	0.92 (0.77-1.06)	0.375
Gait speed <0.8 m/s	371 (29.7)	369 (29.2)	0.853
Frailty Index	0.18 (0.13-0.23)	0.17 (0.12-0.22)	0.004
Frailty Status			0.013
Fit (FI≤0.10)	159 (12.1)	190 (14.5)	
Less fit (0.10<FI≤0.21)	711 (54.3)	745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

The NEW ENGLAND JOURNAL of MEDICINE

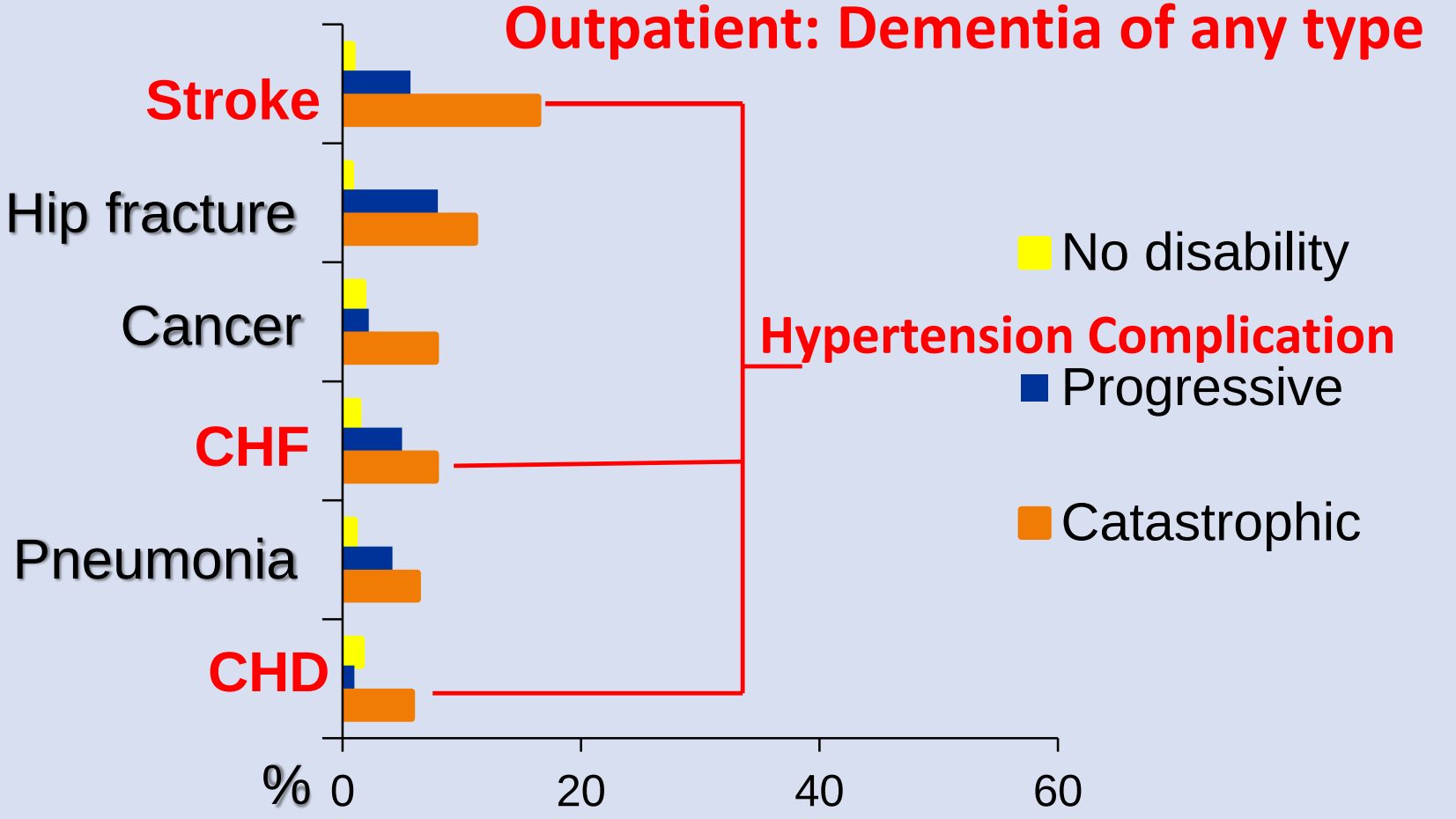
Incidence of the Primary Cardiovascular Outcome and Death from Any Cause in SPRINT

Primary composite outcome includes myocardial infarction, acute coronary syndrome, stroke, heart failure, or cardiovascular death.



The SPRINT Research Group. N Engl J Med 2015;373:2103-2116

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



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

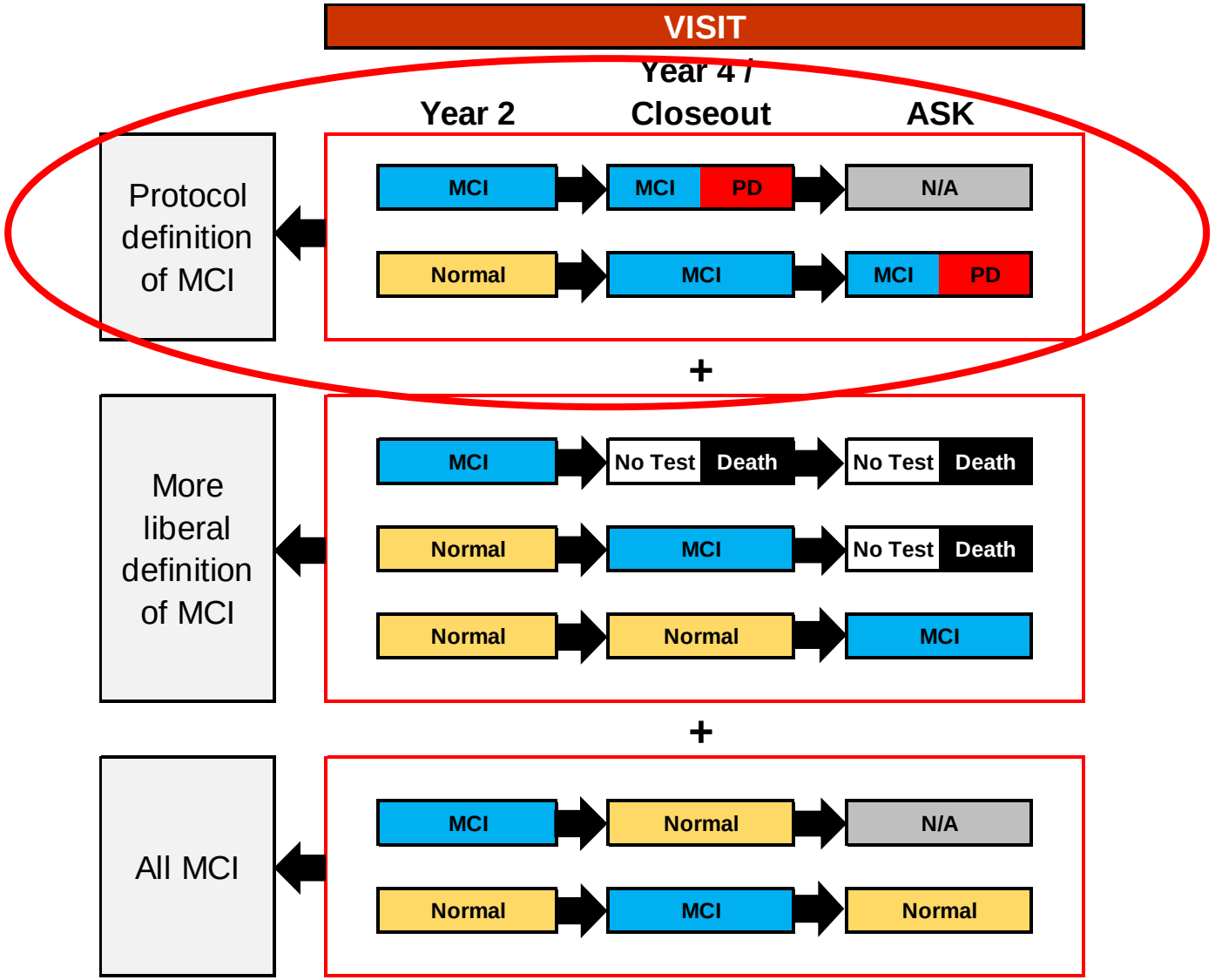
UPDATE IN PROCESS

SPRINT MIND

- Goal was to test whether the **adjudicated occurrence of the following** will be lower in the participants who were randomly assigned to the intensive treatment group (SBP goal < 120 mmHg), compared to those randomly assigned to the standard treatment group (SBP goal < 140 mmHg).
  1. **All-cause probable dementia (PD)**
  2. **Mild Cognitive Impairment (MCI)**
  3. **Composite outcome of PD or MCI**

- Cognitive data collection planned every two years in follow-up

SPRINT MIND Definitions for Mild Cognitive Impairment (MCI) Outcomes



Neurocognitive Battery

COGNITIVE DOMAIN	TEST
Global Functioning	• **Montreal Cognitive Assessment (MoCA)**
Executive Function, *Speed of Processing*	• **Digit Symbol Coding Test** • Trail Making Test
Learning and Memory	• **Logical Memory I** • Hopkins Verbal Learning Test–R
Visual-Spatial Memory	• Modified Rey-Osterreith Figure
Working Memory, Attention, Verbal Fluency	• Digit Span Forward and Backward • Category Fluency-Animals
Language and Naming	• Boston Naming Test (15 item)

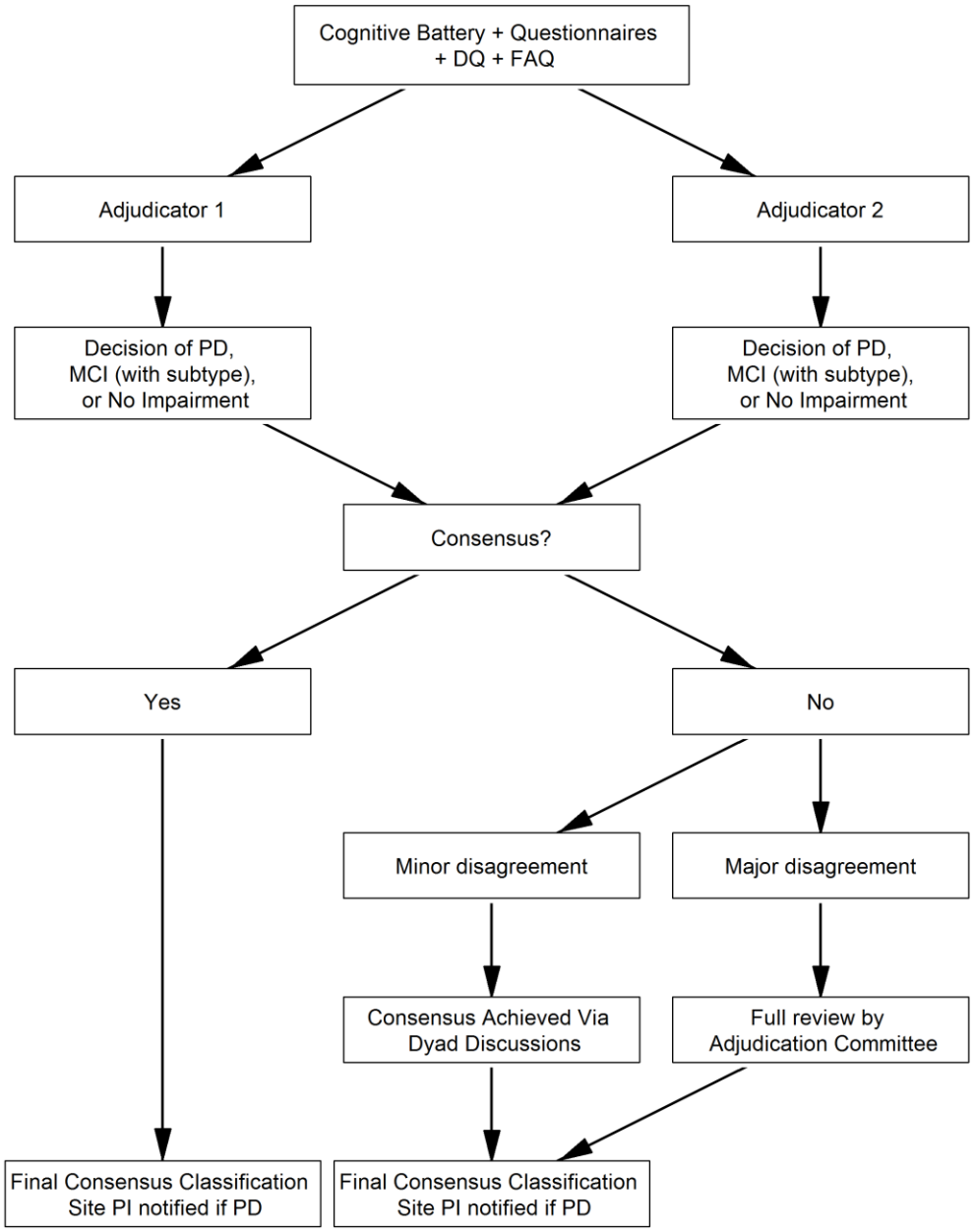
Bold = Tests in Cognitive Screening Battery

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 All participants **PHQ-9**

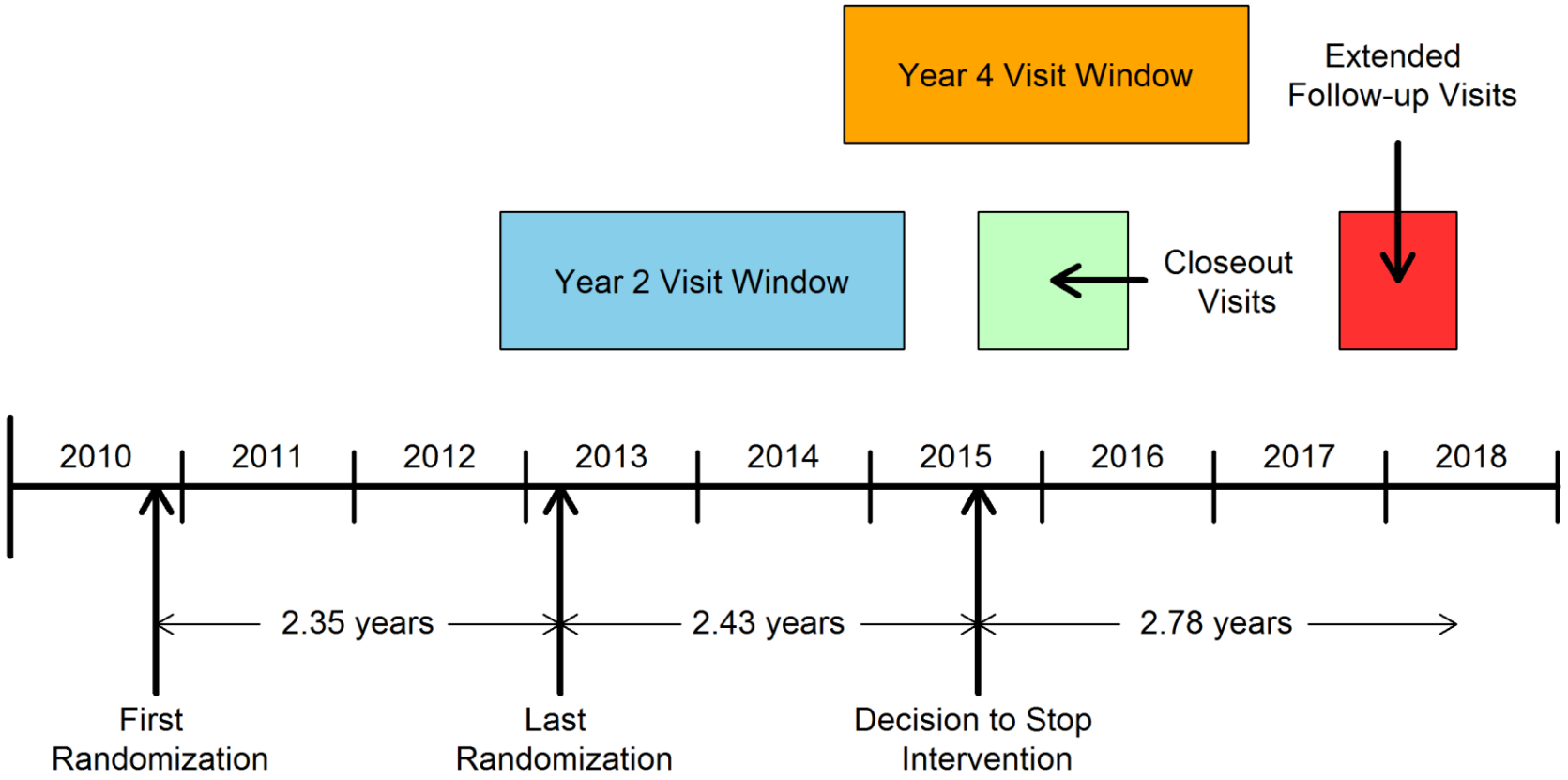
Participants that could not complete in-person testing were administered a validated telephone battery See Rapp *et al.* ***J Am Geriatr Soc*** (2012)

SPRINT-MIND/ASK Adjudication Protocol

>70% agreement between 1st two adjudicators equal to stroke and CHF adjudication agreements

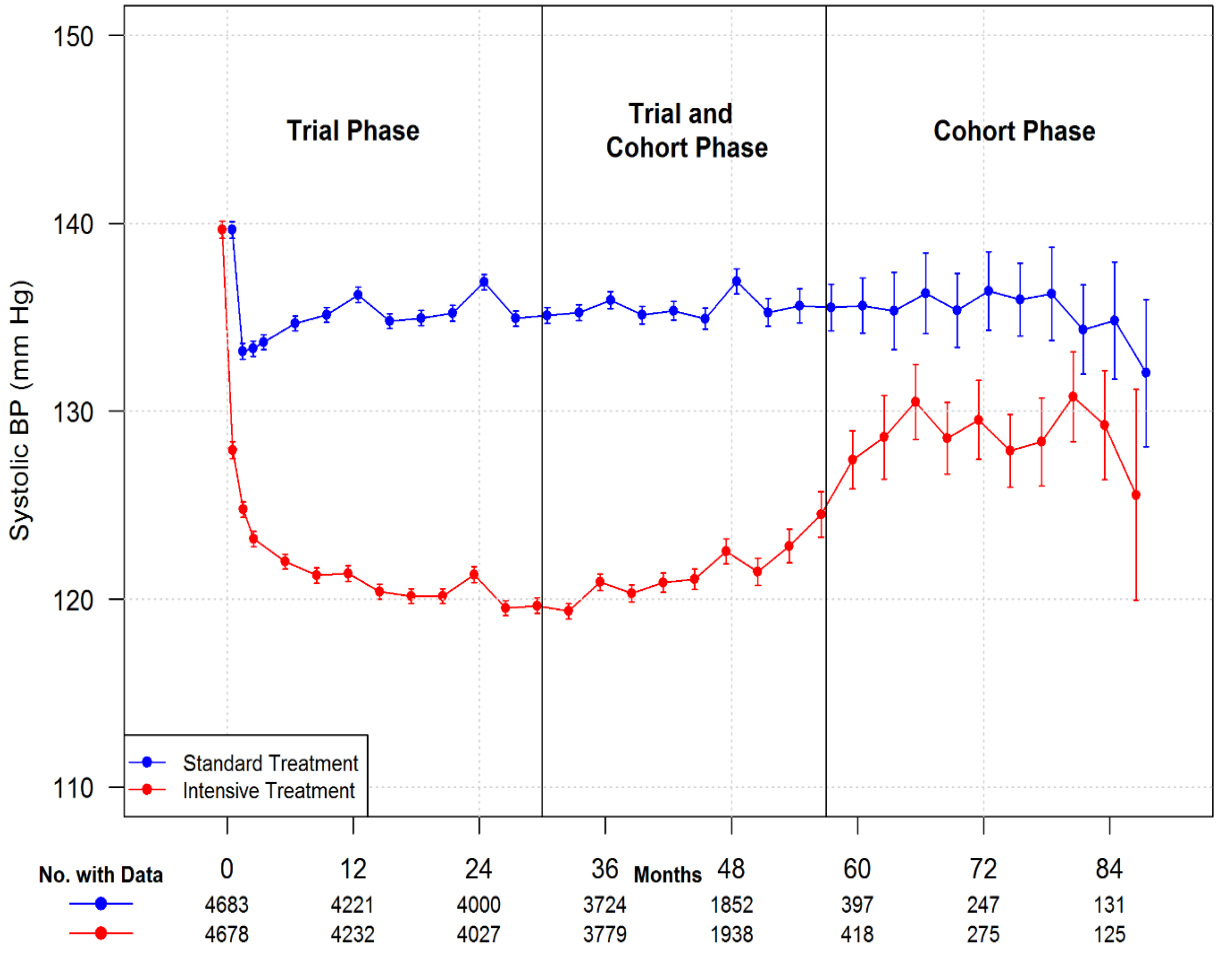


SPRINT Timeline



- Decision to stop intervention occurred at beginning of Year 4 visit window
- With additional observational follow-up, median length of follow-up was 5.1 years, with a median intervention period of 3.3 years

Systolic BP Through Follow-up



Mean Follow-up Systolic Blood Pressure

Standard Treatment
135 mmHg (Intervention Period)
136 mmHg (Closeout Visits)
136 mmHg (Extended Follow-up Visits)

Intensive Treatment
122 mmHg (Intervention Period)
125 mmHg (Closeout visits)
129 mmHg (Extended Follow-up Visits)

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.

Date of download: 2/1/2019

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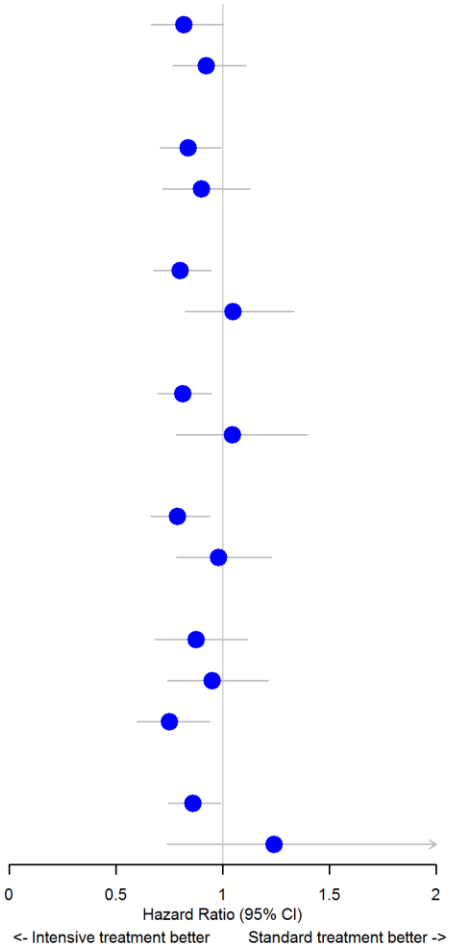
Subgroup Effects for MCI or Probable Dementia

	Intensive treatment No. Events / Total No.	Standard treatment No. Events / Total No.	Hazard Ratio (95% CI)	Interaction P value
Age				**0.32**
<75 years	164 / 3101	202 / 3106	0.82 (0.66, 1.00)	
75 years or older	231 / 1208	253 / 1211	0.92 (0.77, 1.11)	
Sex				**0.63**
Male	248 / 2780	295 / 2810	0.84 (0.71, 0.99)	
Female	147 / 1529	160 / 1507	0.90 (0.72, 1.13)	
Race				**0.09**
Non-Black	256 / 3067	316 / 3027	0.80 (0.68, 0.94)	
Black	139 / 1242	139 / 1290	1.05 (0.82, 1.33)	
History of CVD				**0.14**
No	295 / 3446	361 / 3462	0.81 (0.70, 0.95)	
Yes	100 / 863	94 / 855	1.05 (0.78, 1.40)	
Chronic Kidney Disease				**0.13**
No	232 / 3096	296 / 3125	0.79 (0.66, 0.94)	
Yes	163 / 1213	159 / 1192	0.98 (0.78, 1.23)	
Systolic BP tertiles				**0.43**
132 mm Hg or less	126 / 1481	136 / 1427	0.87 (0.68, 1.12)	
>132 and <145 mm Hg	128 / 1364	136 / 1442	0.95 (0.74, 1.21)	
145 mm Hg or more	141 / 1464	183 / 1448	0.75 (0.60, 0.94)	
Orthostatic hypotension				**0.86**
No	359 / 3996	415 / 4007	0.86 (0.75, 0.99)	
Yes	36 / 313	40 / 310	1.24 (0.74, 2.08)	



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

Primary MRI results

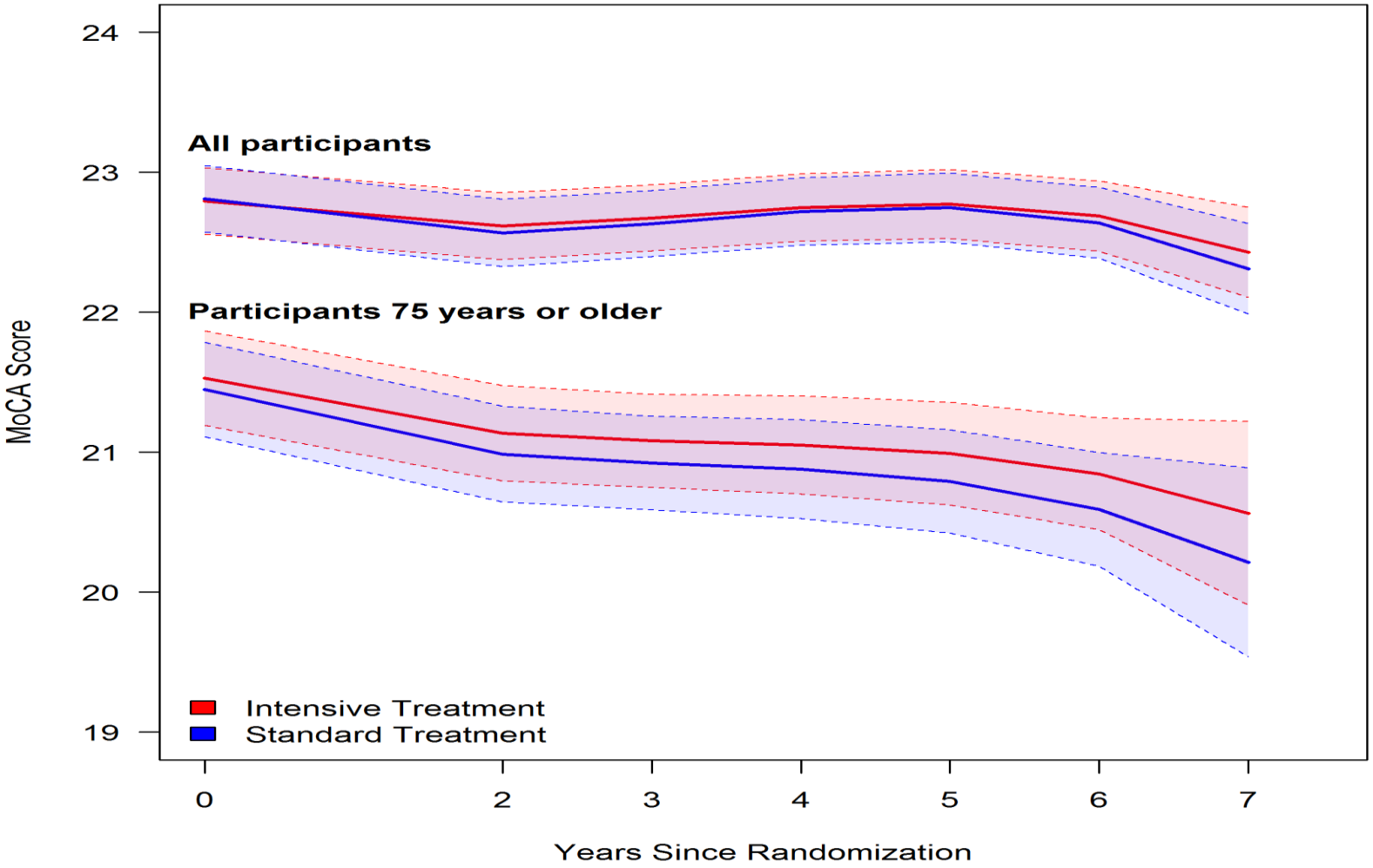
MRI Structural Outcome	**Intensive Treatment** Change (95% CI)	**Standard Treatment** Change (95% CI)	Difference in Change (95% CI)	P Value
Transformed WML Volume, asinh(cm^3)	0.15 (0.11, 0.19)	0.28 (0.24, 0.33)	-0.13 (-0.19, -0.07)	<0.001
WML Volume, cm^3 (RLMM)	0.92 (0.69, 1.14)	1.45 (1.21, 1.70)	-0.54 (-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, asinh inverse hyperbolic sine transformation, and RLMM robust linear mixed model.

Probable Dementia and MCI Incidence by Age: Another reason why prior trials lacked clarity

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

Treatment Group Difference in MoCA Score not Significant



Limitations

- Early termination of SPRINT intervention may have impacted results due to BP increase in the intensive treatment group
- Multi-step cognitive assessment process, triggered based on MoCA score, could have led to under-ascertainment of MCI
- Loss to follow-up with extended follow-up visits could also have led to under-ascertainment of outcomes
- Trial was designed to test treatment goals, and not specific medications, limited ability to infer relative effect of specific antihypertensive medications

Implications

- Intensive blood pressure control is the first RCT intervention to show a reduction in the risk for MCI
- There is no evidence that intensive blood pressure control harms cognition
- SPRINT demonstrated that a diverse population can be recruited, randomized, and assessed in follow-up for cognition over 5 years with acceptable assessment protocol adherence

What about exercise (physical and cognitive), diet, statins?

- Observational studies have shown all of these to be promising but none has yet shown the ability to prevent or delay onset of MCI or dementia
- Current trials are underway:
  - Combining exercise and diet (POINTER) in a randomized trial
  - Atorvastatin randomized trial for primary prevention of MCI/dementia in persons 75+ (PREVENTABLE)

Questions?
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Event Rates and Hazard Ratios for the SPRINT Primary Outcome and its Components in Participants 75 years and Older

Outcome	Intensive N	Intensive %/yr	Standard N	Standard %/yr	HR (95% CI)	p-value
Primary Outcome (any of A-E)	101	2.59	144	3.78	0.67	0.002
(A) All MI	37	0.93	50	1.27	0.73	0.149
(B) Non-MI ACS	17	0.43	17	0.43	1.02	0.949
(C) All Stroke	27	0.67	33	0.83	0.75	0.263
(D) All Heart Failure	34	0.85	56	1.42	0.60	0.020
(E) CVD Death	18	0.44	29	0.72	0.60	0.093
Non-fatal MI	37	0.93	50	1.27	0.73	0.149
Non-fatal Stroke	25	0.62	32	0.81	0.70	0.190
Non-fatal Heart Failure	34	0.85	55	1.40	0.61	0.023
All-cause mortality	73	1.80	106	2.63	0.68	0.013
Primary + All-cause mortality	140	3.58	195	5.10	0.69	0.001

N denotes participants with events

Alternative Strategies for an Aging Society

Delay a specific disease through controlling specific risk factors → Good for the one disease

Current 'FDA' Way of Thinking

Delay aging (by targeting basic molecular processes of aging) → Delay multiple age related functional outcomes & diseases

The New Geroscience Paradigm

Dementia	First symptom	Cognitive pattern	Neurology examination	Neuroimaging	Treatment
AD	Memory loss	Amnesia, word fluency	Normal till late	Posterior temporal/ parietal, PIB positive	Cholinesterase inhibition, NMDA antagonist
FTD	Behavior-apathy, disinhibition, overeating	Loss of executive control	Normal (look for PSP, CBD, ALS)	Anterior frontotemporal insular, basal ganglia	SSRI, NMDA antagonist?
PNFA	Speech, word finding	Non-fluent, dysarthric, apractic speech	Sometimes asymmetric parkinsonism, axial rigidity	Left frontoinsular, basal ganglia	Speech therapy, treat parkinsonism, depression
DLB	Hallucinations, parkinsonism, delirium	Visuospatial, attentional	PD (can be normal at first)	Posterior inferior, Some are PIB positive	Cholinesterase inhibition, carbidopa-levodopa
SD	Word finding, loss of word meaning	Semantic loss, anomia	Normal till later	Anterior temporal	Consider cholinesterase inhibition
Vascular	Variable	Variable, subcortical lesions cause frontal syndrome	Variable, asymmetric, pyramidal deficits	Multiple strokes and/or subcortical white matter lesions	Stroke prevention, consider cholinesterase inhibition
CBD	Asymmetric parkinsonism, PNFA or behavioral	Like FTD or PNFA, sometimes parietal	Asymmetric PD, dystonia, ocular apraxia; alien hand	Frontal, basal ganglia, sometimes parietal	Exercise, treat parkinsonism, treat depression
PSP	Falls, PNFA, behavior	Loss of executive control	Supranuclear gaze palsy, axial rigidity	Midbrain atrophy (variable)	Exercise, treat PD
CJD	Rapid dementia, parkinsonism	Variable	PD, variable	Cortical ribbon, basal ganglia hyperintensity	None

Notes:
SSRI, selective serotonin-reuptake inhibitor; NMDA, *N*-methyl-D-aspartate; other abbreviations as in text.

Table 1.2. Underlying biology of the dementias

Dementia	Histology	Genes for	Molecules	Topography
AD	Amyloid plaques, neurofibrillary tangles	Causal: APP, PS1, PS2 Susceptibility: ApoE4, SIRT-1	Aβ-42, tau	Posterior temporal/parietal
FTD	Gliosis, spongiosus, Pick bodies, ubiquitin-TDP-43	Causal: progranulin, tau VCP, CHMP2B	Tau or TDP-43	Anterior frontotemporal insular, basal ganglia
PNFA	Gliosis, CBD or PSP pathology (see below)	Causal: progranulin, rarely tau, often sporadic	Tau	Left frontoinsular, basal ganglia
DLB	Lewy bodies, nigral loss, often amyloid plaques	Causal: rarely α-synuclein, often sporadic	α-Synuclein, often comorbid; Aβ-42	Posterior parietal, amygdala, basal ganglia, brainstem
SD	Gliosis, ubiquitin-TDP-43	Causal: rarely progranulin, tau, often sporadic	TDP-43	Anterior temporal, amygdala, eventually basal ganglia
Vascular	Infarctions, hyalinization of blood vessels	No specific causal genes	No	Subcortical white matter vulnerable with aging
CBD	Gliosis (cortical, subcortical) coiled tangles, astrocytic plaques	Progranulin, tau, susceptibility polymorphism is H1/H1 tau	Tau	Frontal, basal ganglia, sometimes parietal
PSP	Globose tangles, tufted astrocytes, neurofibrillary tangles	Rarely tau susceptibility polymorphism is H1/H1 tau	Tau	Midbrain, caudate, putamen, brainstem, cerebellum, some frontal
CJD	Astrocytosis, spongiosus	Prion gene mutations	Prion	Cortical, basal ganglia, cerebellum

Notes:
APP, amyloid precursor protein; Aβ-42, amyloid β-42; ApoE, apoprotein E; TDP-43, *TAR DNA*-binding protein 43; PSI, presenilin; CHMP2B, charged multivesicular body protein 2B; VCP, valosin-containing protein; other abbreviations as in text.

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  - 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
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